



Contributions to the Automatic Control of Drug Administration for Anesthesia

Juliana Filipa Carvalho de Almeida

Supervisor: Maria Paula Macedo Rocha Malonek (FEUP)

Co-Supervisor: Teresa Maria de Gouveia Torres Feio Mendonça (FCUP)

Doctoral Program in Electrical and Computer Engineering

July 2, 2018

FACULDADE DE ENGENHARIA DA UNIVERSIDADE DO PORTO

**Contributions to the Automatic Control of Drug
Administration for Anesthesia**

Juliana Filipa Carvalho de Almeida

Dissertation submitted to Faculdade de Engenharia da Universidade do Porto
to obtain the degree of
Doctor Philosophiae in Electronic & Computer Engineering

July 2, 2018

Abstract

Control systems, and, in particular, feedback control systems, have gained increasing importance in biomedical applications over the last years. Such systems have been applied to the automatic administration of anesthetics during surgical procedures, mainly with the purpose of achieving and maintaining adequate levels for relevant physiological parameters.

Among their benefits are avoiding both overdosage and underdosage of the drugs, and consequently minimizing the drug consumption, and reducing the effect of inter and intra individual variability. Focused on these benefits, this thesis aims at giving further contributions to develop control schemes for drug administration during general anesthesia. In this context two important components of anesthesia will be considered: the neuromuscular blockade (NMB) and the depth of anesthesia (DoA). The two components can be simulated by mathematical models with patient parameters. The NMB is modelled as a single-input single-output system whereas the BIS level is modelled as a multiple-input single-output.

In this thesis it is shown to be possible to obtain a good description of the process with a reduced number of patient-dependent parameters in these models. Moreover efficient feedback controllers are designed using these simplified models.

Two control laws will be presented: the first is based on techniques for the control of compartmental systems; the second control law is obtained by solving an optimal control problem (OCP) with a positivity constraint in the input. Due to the complexity introduced by this positivity constraint, the OCP is relaxed into a semi-definite program (SDP) by replacing the original variables by their moments up to a certain order. The optimal values of the moments are then computed by a semi-definite programming solver.

The proposed control techniques are tested in different databases in order to compare their performance and to validate their incorporation in clinical environment, through the platform *GALENO*¹.

¹GALENO - Modeling and Control for personalized drug administration (www.fc.up.pt/galeno)

Resumo

Nos últimos anos, os sistemas de controlo e, em particular, o controlo por retroação tem recebido crescente importância nas aplicações biomédicas. Um exemplo dessas aplicações é o controlo automático da administração de fármacos em anestesia geral, com o objetivo de alcançar e manter determinados níveis fisiológicos.

Entre as suas vantagens, está a de evitar a sob-dosagem e a sobre-dosagem e, consequentemente, reduzir o consumo de fármacos e também o efeito da variabilidade inter e intra individual. Desta forma, o objetivo desta tese é contribuir para o desenvolvimento de estratégias de controlo para a administração automática durante anestésias gerais. Neste contexto, existem duas importantes componentes a considerar: o nível de relaxamento (NMB) e a profundidade anestésica (DoA). Estas duas componentes podem ser obtidas através de modelos matemáticos. Modelos estes, que são dependentes de parâmetros do paciente. O NMB pode ser representado por um modelo de uma entrada e uma saída e o DoA por um modelo de múltiplas entradas e uma saída.

Nesta tese é provado que é possível obter uma boa descrição dos processos com um número reduzido de parâmetros dependentes do paciente. Os sistemas de controlo apresentados aqui serão desenvolvidos tendo por base estes modelos simplificados.

Duas leis de controlo serão apresentadas: a primeira é baseada em técnicas de controlo para sistemas compartimentais; a segunda lei de controlo é obtida através da solução de um problema de controlo ótimo com restrições de positividade. Devido à complexidade imposta por essa restrição, o problema de controlo ótimo será relaxado num problema de programação semi-definida através de uma mudança de variável. Mais concretamente, as variáveis originadas serão substituídas pelas medidas matemáticas chamadas momentos. Os valores ótimos dos momentos serão determinados por um *solver* de programação semi-definida.

As técnicas desenvolvidas foram testadas em diferentes bases de dados com o objetivo de comparar os seus desempenhos e de validar a sua incorporação em ambiente clínico através da plataforma *GALENO*².

²GALENO - Modeling and Control for personalized drug administration (www.fc.up.pt/galeno)

Agradecimentos

First of all, I owe my deepest gratitude to my supervisors Professor Paula Rocha and Professor Teresa Mendonça by their constant guidance, support and feedback given during these last four years. I also would like the friendship, the positive words and all advices given.

I am grateful to Professor Luis Rodrigues for inviting me to work with him at Concordia University, Montreal (Canada) and for offering me the opportunity to acquire knowledge with his groups. It was a pleasure to have lived in Montreal.

I would also thank you the Portuguese Foundation for Science and Technology for financial supporting of this thesis with the grant SFRH/BD/87128/2012, as well the Project POCI-01-0145-FEDER-006933 - SYSTEC - Research Center for Systems and Technologies - funded by FEDER funds through COMPETE2020 - Operational Programme Factors of Competitiveness – and by FCT - Portuguese Foundation for Science and Technology. I also like to acknowledge the support of the Natural Sciences and Engineering Research Council of Canada by the financial support given during my stay in Canada.

I thank my Lab colleagues in the Department of Electrical and Computer Engineering for being a great team during this last year, for the good times and for their friendship.

A special thanks for the ones (they know who they are) who were closer to me in different stages of this journey.

Em especial, dedico e agradeço aos meus pais por me terem proporcionado esta caminhada, estando sempre presentes e aceitando sempre as minhas escolhas.

Juliana Almeida

"Straight ahead you can't go very far"

Antoine de Saint-Exupéry

Contents

1	Introduction	1
1.1	Overview of general anesthesia	2
1.2	Automatic drug delivery in anesthesia	3
1.3	Thesis contributions	6
2	Compartmental models in anesthesia	7
2.1	Compartmental models	7
2.2	PK/PD compartmental based models for drug effect	9
2.2.1	Model for <i>atracurium</i> - NMB case	9
2.2.2	Model for <i>remifentanil</i> and <i>propofol</i> - BIS case	11
2.3	Reduced parameter compartmental models for drug effect	13
2.3.1	Model for <i>atracurium</i> - NMB case	14
2.3.2	Model for <i>remifentanil</i> and <i>propofol</i> - BIS case	17
3	System Identification	21
3.1	Introduction	21
3.2	NMB model identification	22
3.3	BIS model identification	25
4	Simplified control applied in general anesthesia	29
4.1	Positive control law	29
4.1.1	Control for <i>atracurium</i> - NMB case	31
4.1.2	Control of <i>remifentanil</i> and <i>propofol</i> - BIS case	34
4.2	Simplified positive control law	37
4.2.1	Simplified control for <i>atracurium</i> - NMB case	38
4.2.2	Simplified control for <i>remifentanil</i> and <i>propofol</i> - BIS case	41
4.3	Control scheme with parameter identification	43
4.3.1	Simplified control scheme for <i>atracurium</i> - NMB case	44
4.3.2	Simplified control scheme for <i>remifentanil</i> and <i>propofol</i> - BIS case	48

5	Controllers based on optimal control	53
5.1	Optimal control for <i>atracurium</i> - NMB case	57
5.2	Optimal control for <i>remifentanyl</i> and <i>propofol</i> - BIS case	65
6	Conclusions	75
6.1	Comparison of the NMB case results	75
6.2	Comparison of the BIS case results	76
6.3	Clinical environment	77
6.4	Main contributions and future work	78
A	PK/PD parameters for the <i>atracurium</i> - NMB model	79
B	Parameters values for the reduced NMB model	83
C	Real doses of <i>atracurium</i> and the corresponding NMB level	85
D	PK/PD parameter values for the BIS model	91
D.1	Schneider and Minto models	91
D.1.1	Schnider's model	91
D.1.2	Minto's model	92
D.2	Database	92
E	Parameters values for the reduced BIS model	95
	References	97

List of Figures

1.1	The left figure shows the sensor position to measure the NMB level, whereas the right figure shows the place where the BIS sensor is set.	3
1.2	Automatic system for drug administration during general anesthesia.	3
2.1	A compartment of a compartmental system.	7
2.2	Block diagram for the Wiener PK/PD model.	9
2.3	PK/PD compartmental model for the muscle relaxant <i>atracurium</i> . The central compartment is composed by the main organs heart, liver, lungs, kidney and by the blood, and the peripheral compartment corresponds, for instance, to the fat tissue and the cerebrospinal fluid. In this case the effect compartment corresponds to the muscle tissue.	10
2.4	Impulse effect concentration (upper plot) and the impulse NMB level (bottom plot) to an initial <i>bolus</i> of $500\mu g.kg^{-1}$ of the muscle relaxant <i>atracurium</i> for the simulated patient number 98.	11
2.5	PK/PD compartmental based model for both <i>propofol</i> and <i>remifentanil</i>	12
2.6	Simulated BIS level response to a <i>bolus</i> (modeled as an impulse) of <i>propofol</i> combined with a <i>bolus</i> (impulse) of <i>remifentanil</i>	13
2.7	Block diagram that relates the drug dose of muscle relaxant, $u(t)$, with the NMB response, $y_{NMB}(t)$, according Silva et al. (2012).	14
2.8	Diagram block that represents the artificial compartmental structure of the state-space realization (2.12) of the reduced model for the NMB response to <i>atracurium</i>	15
2.9	Impulse standardized effect concentration (upper plot) and impulse NMB response (bottom plot) to an initial <i>bolus</i> of $500\mu g.kg^{-1}$ of <i>atracurium</i> for the simulated patient number 98.	16
2.10	NMB impulse responses obtained through the reduced model (red line) and through the PK/PD model (blue line).	16
2.11	Block diagram that relates the drug doses of the propofol, $u^R(t)$, and remifentanil, u^P , with the BIS level, $y_{BIS}(t)$, according to Silva et al. (2014b).	17
2.12	Impulse responses of the BIS level when <i>propofol</i> and <i>remifentanil</i> are administered as hypnotic and analgesic, respectively, obtained with the reduced model (red line) and with the PK/PD model (blue line).	19

3.1	NMB level estimated by the EKF (blue line) and the one collected during a general anesthesia (red dashed line).	25
3.2	Parameter estimation performed by the EKF.	25
3.3	BIS level estimated by the EKF (blue line) and the one collected during a general anesthesia (red dashed line).	27
3.4	Parameter estimation performed by the EKF for the BIS model.	28
4.1	NMB level evolution when the drug dose is determined by the positive control law. The star represents the time instant when the controller action begins.	33
4.2	The upper plot presents the NMB level evolution when the drug dose is determined by the positive control law for the hundred models and the bottom plot presents the average response signal of these hundred models.	34
4.3	System mass evolution for the <i>propofol</i> model and for the <i>remifentanil</i> model. . .	36
4.4	BIS level evolution when the drug doses of <i>propofol</i> and <i>remifentanil</i> are determined by the positive control laws.	37
4.5	BIS level evolution when the drug doses of <i>propofol</i> and <i>remifentanil</i> are determined by the positive control laws for the eighteen cases of Appendix E (upper plot) and the average of these eighteen signals (bottom plot). The dashed line represents the reference BIS level.	37
4.6	NMB level evolution for the scenarios (1) and (2) for patient number 2 for the real dose administered during surgery, consisting of an initial <i>bolus</i> followed by a second <i>bolus</i> at time instant $t = 30$ min.	39
4.7	Mean value of NMB level evolution for the scenarios (1) and (2) for the hundred simulated models.	40
4.8	Comparison between the NMB level for the patient 17 obtained when the drug is determined by the positive control law (blue line) and the NMB level obtained when the drug is determined by the simplified positive control law (red line). . . .	40
4.9	Comparison between the NMB level obtained when the drug is determined by the positive control law (blue line) with $\lambda = 0.2$ and the NMB level obtained when the drug is determined by the simplified positive control law (red line) with $\lambda = 0.5$. . .	41
4.10	BIS level evolution for the scenarios (1) and (2).	42
4.11	Average BIS level response evolution under scenarios (1) and (2) for the eighteen simulated models.	43
4.12	Comparison between the BIS level obtained when the drug doses are determined by the positive control laws (blue line) and the BIS level obtained when the drug doses are determined by the simplified positive control laws (red line).	43
4.13	Comparison between the BIS level obtained when the drug doses are determined by the positive control laws (blue line) with $\lambda = 5$ and the BIS level obtained when the drug doses are determined by the simplified positive control laws (red line) with $\lambda = 10$	44

- 4.14 Block diagram of the control scheme where the patient dependent parameters are identified by the EKF algorithm. 44
- 4.15 In the upper plot the *atracurium* dose given by the control scheme (red line) is represented and compared with the dose administered by the clinician in a general anesthesia (blue line). The bottom plot shows the corresponding NMB level. y_{NMB}^{SC+id} represents the NMB level obtained by applying the simplified control with parameter identification and y_{NMB}^{real} represents the real NMB level collected during the general anesthesia procedure. 45
- 4.16 Total amount of *atracurium* administered during the surgery (red star) and the total amount determined by the control scheme (blue bullet). $\sum u^{SC+id}$ represents the total amount dose obtained by the simplified control with parameter identification and $\sum u^{real}$ represents total amount of the real dose administered during general surgeries. 46
- 4.17 Mean of the real NMB level between the time instants t_i and t_f (red star) and mean of the simulated NMB level in the same time interval (blue bullet). t_i is the first time instant where the response is lower than 10% and t_f is the time instant when the surgery ends. $\bar{y}_{NMB}^{SC+id}$ represents the mean of the NMB level between in the time interval $[t_i, t_f]$ obtained by the simplified control with parameter identification and $\bar{y}_{NMB}^{real}$ represents the mean of the real NMB level between in the time interval $[t_i, t_f]$. 47
- 4.18 Cost value obtained for the real cases (blue bullet) and the cost value obtained for the control scheme (red star). J^{SC+id} represents the cost value obtained using the signals obtained by the simplified control with parameter identification and J^{real} represents the cost value obtained using the real signals obtained during general surgeries. 47
- 4.19 Total amount of *atracurium* administered during the surgery (red star) and the total amount determined by the control scheme (blue bullet) when the NMB reference level is taken to be equal to the mean of the real NMB level between the time instants t_i and t_f . t_i is the first time instant where the response is lower than 10% and t_f is the time instant when the surgery ends. 48
- 4.20 The upper plot shows the BIS level obtained when the profile of the drug doses represented in the bottom plot are administered. y_{BIS}^{SC} represents the BIS level obtained using the simplified controller, y_{BIS}^{real} is the real BIS level signal and y_{BIS}^{ref} is the BIS reference level; u^{pSC} and u^{preal} represent the *propofol* doses obtained by the simplified controllers and the ones obtained for the real cases (in clinical environment), respectively, and u^{RSC} and u^{Rreal} represent the *remifentanyl* doses obtained by the simplified controllers and the ones obtained for the real cases (in clinical environment), respectively. 49

- 4.21 The left plot represents the total amount of *propofol* administered during the surgery (red star) and the total amount determined by the control scheme (blue bullet). The right plot presents the total amount of administered *remifentanyl* in the same conditions. $\sum u^{pSC+id}$ and $\sum u^{preal}$ represent the *propofol* doses obtained by the simplified controllers with parameter identification and the ones obtained for the real cases (in clinical environment), respectively, and $\sum u^{RSC+id}$ and $\sum u^{Rreal}$ represent the *remifentanyl* doses obtained by the simplified controllers with parameter identification and the ones obtained for the real cases (in clinical environment), respectively. 50
- 4.22 Mean of the real BIS level between the time instants t_i and t_f (red star) and mean of the simulated NMB level in the same time interval (blue bullet). t_i is the first time instant where the response is lower than 50% and t_f is the time instant when the surgery ends. $\bar{y}_{BIS}^{SC+id}$ represents the mean of the BIS level between in the time interval $[t_i, t_f]$ obtained by the simplified control with parameter identification and $\bar{y}_{BIS}^{real}$ represents the mean of the real BIS level between in the same time interval. . 51
- 4.23 Cost values obtained for the real cases (blue bullet) and for the control scheme (red star). J^{SC+id} represents the cost value obtained using the signals obtained by the simplified control with parameter identification and J^{real} represents the cost value obtained using the real signals obtained during the general surgery. 51
- 4.24 Comparison between the BIS response when the parameters are identified at $t^* = 4min$ and $t^* = 8min$ and the BIS response when the parameters are only identified at $t^* = 4min$. y_{BIS}^{real} represents the real BIS level collected during the general anesthesia procedure, y_{BIS}^{SC+id} represents the BIS level obtained by applying the simplified control with parameter identification, $y_{BIS}^{SC+id+id}$ is the signals obtained where the parameter identification is adjusting at $t^* = 8min$, y_{BIS}^{real} represents the BIS reference level and + is the time instant where the parameter identification is adjusting. 51
- 4.25 Comparison between the BIS response when the parameters are identified at $t^* = 4min$ and $t^* = 8min$. The two markers in the x-axis, respectively, indicate the instants when the parameters and the BIS reference level were readjusted. y_{BIS}^{real} represents the real BIS level collected during the general anesthesia procedure, $y_{BIS}^{SC+id+id}$ represents the BIS level obtained by readjusting of the simplified control and y_{BIS}^{ref} represents the BIS reference level. 52
- 5.1 Simulation of the NMB level response (upper plot) using the state-feedback control (bottom plot) given by the moment relaxation design method. 61
- 5.2 Simulation of the NMB level response (upper plot) using the state-feedback control (bottom plot) given by the moment relaxation design method, both for the scenarios 1 (u and y_{NMB}) and 2 (u^{SC} and y_{NMB}^{SC}) 62

- 5.3 Simulation of the NMB level response (upper plot) using the state-feedback control (bottom plot) given by the moment relaxation design method. y_{NMB}^{SC+id} represents the NMB level obtained using the state-feedback control with parameter identification, y_{NMB}^{real} is the real NMB signal obtained during a general surgery and y_{NMB}^{ref} is the reference NMB level. 63
- 5.4 Total amount of *atracurium* administered during the surgery (red star) and the total amount determined by the control scheme (blue bullet). $\sum u^{SC+id}$ is the total amount of *atracurium* administered using the state-feedback control with parameter identification and $\sum u^{SC}$ is the total amount of *atracurium* administered to the 10 real cases of the database of Appendix C 64
- 5.5 Mean of the real NMB level between the time instants t_i and t_f (red star) and mean of the simulated NMB level in the same time interval (blue bullet) for 10 cases of the database of Appendix C. t_i is the first time instant where the response is lower than 10% and t_f is the time instant when the surgery ends. $\bar{y}_{NMB}^{SC+id}$ is the mean of the NMB level obtained using the state-feedback control with parameter identification in that time interval and $\bar{y}_{NMB}^{real}$ is the mean of the real NMB level for the 10 cases of the database of Appendix C. 64
- 5.6 Cost value obtained for the real cases (blue bullet) and the cost value obtained for the control scheme (red star) for 10 cases of the database of Appendix C. J^{SC+id} is the cost value for the signals obtained using the state-feedback control with parameter identification and J^{SC} is the cost value obtained using the real signals collected in the clinical practice. 65
- 5.7 Simulation of the BIS level response, y_{BIS} , (upper plot) using the state-feedback control (bottom plot) given by the moment relaxation method designed with $\xi = \xi_8 = 0.0860$, $\eta = \eta_8 = 0.0212$, $m = m_8 = 1.4203$ and $\zeta = \zeta_8 = 0.9780$ 70
- 5.8 Comparison between the BIS level response, y_{BIS} , (upper plot) using the state-feedback control, u , (bottom plot) given by the moment relaxation method designed with $\xi = \xi_8 = 0.0860$, $\eta = \eta_8 = 0.0212$, $m = m_8 = 1.4203$ and $\zeta = \zeta_8 = 0.9780$ and the BIS level y_{BIS}^{SC} using the simplified state-feedback control u^{SC} , *i.e.*, using the state-feedback control designed with $\xi = \bar{\xi} = 0.0759$, $\eta = \bar{\eta} = 0.5825$, $m = m_8 = 1.4203$ and $\zeta = \zeta_8 = 0.9780$ 70
- 5.9 Simulation of the BIS level response (upper plot) using the state-feedback control (bottom plot) given by the moment relaxation method designed using $\xi = \bar{\xi} = 0.0759$, $\eta = \bar{\eta} = 0.5825$, $m = m(t^*) = 1.998$ and $\zeta = \zeta(t^*) = 1.001$. $\sum u^{pSC+id}$ and $\sum u^{preal}$ represent the *propofol* doses obtained by the simplified state-feedback controllers with parameter identification and the ones obtained for the real cases (in clinical environment), respectively, and $\sum u^{RSC+id}$ and $\sum u^{Rreal}$ represent the *remifentanyl* doses obtained by the simplified state-feedback controllers with parameter identification and the ones obtained for the real cases (in clinical environment), respectively. 71

5.10	Total amount of <i>propofol</i> and of <i>remifentanyl</i> administered during the surgery (red star) and the total amount determined by the control scheme (blue bullet). $\sum u^{pSC+id}$ and $\sum u^{preal}$ represent the <i>propofol</i> doses obtained by the simplified controllers with parameter identification and the ones obtained for the real cases (in clinical environment), respectively, and $\sum u^{rSC+id}$ and $\sum u^{rreal}$ represent the <i>remifentanyl</i> doses obtained by the simplified state-feedback controllers with parameter identification and the ones obtained for the real cases (in clinical environment), respectively.	72
5.11	Mean of the real BIS level between the time instants t_i and t_f (red star) and mean of the simulated NMB level in the same time interval (blue bullet). t_i is the first time instant where the response is lower than 50% and t_f is the time instant when the surgery ends. $\bar{y}_{BIS}^{SC+id}$ represents the mean of the BIS level between in the time interval $[t_i, t_f]$ obtained by the simplified state-feedback control with parameter identification and $\bar{y}_{BIS}^{real}$ represents the mean of the real BIS level between in the same time interval.	73
5.12	Cost value obtained for the real cases (blue bullet) and the cost value obtained for the control scheme (red star). J^{SC+id} represents the cost value obtained using the signals obtained by the simplified state-feedback control with parameter identification and J^{real} represents the cost value obtained using the real signals obtained during the general surgery.	73
6.1	Cost value obtained for the control scheme when the controller is given by the positive control law, J^{PCL} , (red star), the cost value obtained for the control scheme when the controller is the solution of the optimal control problem J^{OCP} , (blue star) for the NMB level and the cost value obtained using the real signals J^{real} (green cross).	76
6.2	Cost value obtained for the control scheme when the controller is given by the positive control law, J^{PCL} , (red star), the cost value obtained for the control scheme when the controller is the solution of the optimal control problem J^{OCP} , (blue star) for the BIS level and the cost value obtained using the real signals J^{real} (green cross).	77
C.1	NMB level and the <i>atracurium</i> dose profile of the patient number 1.	85
C.2	NMB level and the <i>atracurium</i> dose profile of the patient number 2.	86
C.3	NMB level and the <i>atracurium</i> dose profile of the patient number 3.	86
C.4	NMB level and the <i>atracurium</i> dose profile of the patient number 4.	87
C.5	NMB level and the <i>atracurium</i> dose profile of the patient number 5.	87
C.6	NMB level and the <i>atracurium</i> dose profile of the patient number 6.	88
C.7	NMB level and the <i>atracurium</i> dose profile of the patient number 7.	88
C.8	NMB level and the <i>atracurium</i> dose profile of the patient number 8.	89
C.9	NMB level and the <i>atracurium</i> dose profile of the patient number 9.	89
C.10	NMB level and the <i>atracurium</i> dose profile of the patient number 10.	90

List of Tables

2.1	Values used to simulate the linear model of the PK/PD model both for <i>propofol</i> and for <i>remifentanyl</i> , corresponding to the Schnider model and the Minto model, respectively, for a 56 year-old female with 160 <i>cm</i> of height and 88 <i>kg</i> of weight. .	13
5.1	Exponents β for test function $v(\hat{x})$	58

List of Abbreviations and Symbols

AMG	Acceleromyography
BIBO	Bounded-Input Bounded-Output
BIS	Bispectral Index
EEG	Electroencephalogram
EMG	Electromyography
DoA	Depth of Anesthesia
EKF	Extended Kalman Filter
IoC	Index of Consciousness
LQR	Linear Quadratic Regulator
LQ	Linear Quadratic
KF	Kalman Filter
MISO	Multiple-Input Single-Output
MMG	Mecanomyography
NMB	Neuromuscular Blockade
PID	Proportional-Integral-Derivative
PK	Pharmacokinetics
PD	Pharmacodynamincs
PK/PD	Pharmacokinetics/Pharmacodynamics
OCP	Optimal Control Problem
OLARD	On Line tuned Algorithm for Recovery Detection
RM	Reduced Model
SC	Simplified Control
SISO	Single-Input Single-Output
SDP	Semi-definite Program
SE	Spectral Entropy
TCI	Target-Controlled Infusion
TOF	Train-of-Four
T1	Frist Single Response

Introduction

Control systems, and, in particular, feedback control, have gained increasing importance in biomedical applications over the last years. Feedback control systems use information from measurements in order to determine a suitable input signal that achieves a desired goal. Such systems have been applied to the automatic administration of anesthetics during surgical procedures, mainly with the purpose of achieving and monitoring adequate levels for relevant physiological parameters, Mendonça and Lago (1998), Lago et al. (2000). Among their benefits are avoiding both overdosage and underdosage of the drugs, minimizing the drug consumption, and reducing the effect of inter and intra individual variability. Focused on these benefits, this thesis aims at giving further contributions to develop control schemes for drug administration during general anesthesia. In this context two important components of anesthesia will be considered: the neuromuscular blockade (NMB) and the depth of anesthesia (DoA).

In the clinical practice, anesthetics are administered following standard dosing guidelines often based on an average patient, Bailey and Haddad (2005). The common procedure is to administer an initial dose, observe the response, and adjust the dose according to the desired output (e.g., NMB and BIS levels). To reach an individualized dose the anesthesiologists need to understand the pharmacokinetics (PK) and pharmacodynamics (PD) of the drugs in use, as well as possible drug interaction. Pharmacokinetics studies the relation between the administrated drug dose and the obtained plasmatic drug concentration, taking into account the absorption, the distribution and the biotransformation of the drugs; pharmacodynamics relates the plasmatic drug concentration with the actual drug effect on a patient, *i.e.*, the physiological and biochemical effects of drugs and their mechanism of action. The PK/PD models are a mathematical description of these relationships and are the most used models Gambus and Trocóniz (2015). However, they involve a high number of total patient-dependent parameters and the poor excitation of the input signals (associated with this application) is not enough to achieve a good performance of the identification methodologies. In order to overcome this difficulty, new Wiener models (*i.e.*, consisting of a dynamic linear part followed by a static nonlinearity) for the effect of the drugs in general anesthesia were proposed in Silva et al. (2012), Silva et al. (2014b). These models have a parsimonious structure containing a small number of patient-dependent parameters to describe the system. In

Silva et al. (2012) a two-parameter single-input single-output (SISO) model for the induction neuromuscular blockade by means of *rocuronium* is proposed, and a four-parameter multiple-input single-output (MISO) for the effect of *propofol* and *remifentanyl* on the depth of anesthesia model is proposed in Silva et al. (2014b). Recently, it was proven in Almeida et al. (2016) and Almeida et al. (2017) that it is possible to design a positive control law using only the parameters associated to the nonlinear part of such models. These simplified models were the motivation for the development of new algorithms to control the effect of the drugs during a general anesthesia to be integrated in the Galeno platform. This platform was developed in the framework of the Portuguese Science and Technology funding agency (FCT) project Galeno and incorporates several identification and control procedures for automation in the administration of anesthetics.

1.1 Overview of general anesthesia

General anesthesia comprises three components: hypnosis, analgesia and muscle relaxation. To achieve these goals, the anesthesiologists administer several drugs while simultaneously maintaining all the vital functions, thus enabling a patient to undergo surgical procedures that would otherwise be impossible or very painful to tolerate.

Muscle relaxation implies the loss of movement, which is essential for patient intubation, to facilitate the access to internal organs, and to avoid movement responses as a result of surgical stimuli. This is achieved by the administration of muscle relaxants that block the neuromuscular activity. The NeuroMuscular Blockade (NMB) level is measured from an evoked muscle response at the hand of the patient subject to electrical stimulation of the adductor pollicis muscle through supra maximal train-of-four (TOF) stimulation of the ulnar nerve; it can be registered by electromyography (EMG), mecanomyography (MMG) or acceleromyography (AMG), Hemmerling (2004), McGrath and Hunter (2006). The NMB level corresponds to the first single response (T1) calibrated by a reference twitch, ranging between 100% (full muscular activity) and 0% (totally paralysis).

Hypnosis is defined as the absence of consciousness and the inability of the patient to recall intraoperative events. This is achieved by the administration of hypnotics and is measured by the electroencephalographic activity. The electroencephalogram (EEG)-derived indices used to infer the level of hypnosis of a patient are: the Spectral entropy (SE), Vartiö-Oja et al. (2004), the Index of Consciousness (IoC), Jensen et al. (2008), and the Bispectral Index (BIS), Gan et al. (1997). The most widely used index is the BIS. It is related to the responsiveness level and the probability of recalling intraoperative events and it ranges from 97.7 (fully awake and alert state) to 0 (totally absence of brain activity). During general anesthesia the adequate BIS level varies between 40 and 60.

Finally, analgesia is obtained by the administration of analgesics and allows the loss of the pain. There is no single measure to analyze this condition; the anesthesiologists estimate the analgesia level based on autonomic reactions, such that changes in blood pressure and heart rate,

sweating, pupil reactivity and the presence of tears, Guignard (2006). The hypnotics and analgesics interact in such way that their effect is enhanced when administered together. The depth of anesthesia (DoA) takes into account the combined levels of hypnosis and analgesia, and the BIS is the index used to evaluate this feature.

The following figure shows the position of the sensors measure for the NMB and BIS, respectively.

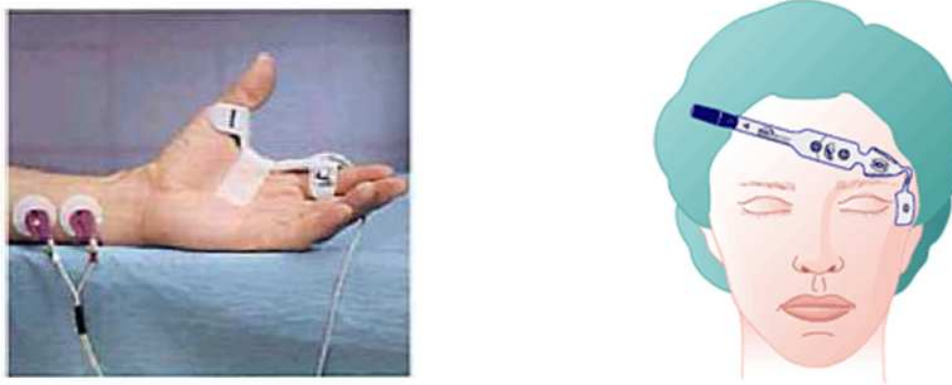


Figure 1.1: The left figure shows the sensor position to measure the NMB level, whereas the right figure shows the place where the BIS sensor is set.

1.2 Automatic drug delivery in anesthesia

The development of automation techniques for anesthesia has been growing in last decade. The use of an automatic system to monitor and control the drug administration during the surgery leads to two benefits: the improvement of the global performance of the process in terms of safety, cost reduction and patient comfort, and the possibility of releasing the anesthetist from some routine tasks so that he/she can better concentrate on the state of the patient.

Figure 1.2 shows the feedback control scheme applied to drug delivery in anesthesia. In the beginning the clinicians impose a desired reference effect and the control algorithms should compute the adequate amount of drug(s) to achieve this set-point. If the measured effect does not correspond to the desired one, the controller should automatically adapt the drug(s) dosage.

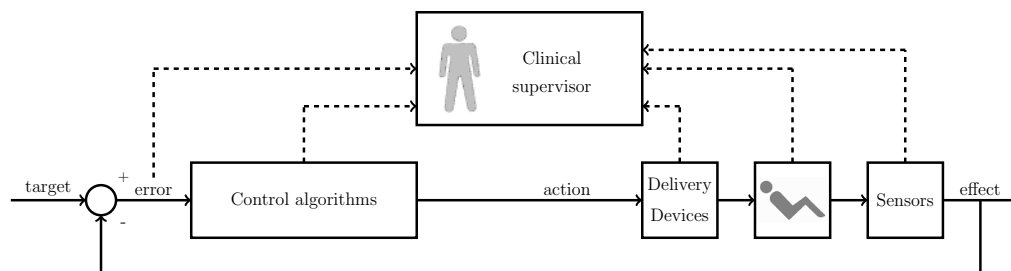


Figure 1.2: Automatic system for drug administration during general anesthesia.

In the last decades, researchers have been improving the performance of the control algorithms to be included in a system like the one in Figure 1.2. Regarding the control of the NMB level, the initial studies on feedback control for the administration of muscle relaxants started around thirty years ago, Brown et al. (1980), Jaklitsch and Westenskow (1987), Ritchie et al. (1985). A constant gain Proportional-Integral-Derivative (PID) controller was developed in Lago et al. (1998). However the patient's response variability is high and, to avoid this issue, methods for online tuning of PID controllers to the individual patient dynamics were implemented Mendonça and Lago (1998), Silva et al. (2005), Lago et al. (2000). An alternative method to tackle the high uncertainty in neuromuscular blockade model is the use of multiple model switching control strategy as in Mendonça et al. (2002), Neves et al. (2009) where a bank of suitable stabilising controllers, each of them tuned for a different model, was used. More recently, the same strategy was considered but using a different bank of controllers. This bank is constituted by positive controllers for feedback stabilisation of positive compartmental systems that guarantee the convergence of the total system mass to a set-point which, in turn, guarantees the tracking of a desired NMB level, Teixeira et al. (2014).

With respect to the control of the depth of anesthesia, the first system to automatically achieve a predefined individualized concentration of anesthetics in the plasma, and hence a desired drug effect, was the target-controlled infusion (TCI), Glen (1998). Here the anesthesiologist sets the desired theoretical (target) concentration of the drug, and the device calculates the amount of drug to be administered in order to obtain specific concentration. The infusion rate is computed based on population models for the PK/PD of the drugs. More concretely, the TCI devices incorporate two models for the hypnotic propofol: the Marsh model, Marsh et al. (1991) and the Schnider model, Schnider et al. (1998); and one model for the opioid remifentanyl: the Minto model, Minto et al. (1997). These models use information as the patient's age, height, weight and gender. However, due to some inaccuracy in the patient's dose-effect relationship that is not covered by the linear PK/PD models, the anesthesiologists have an active role to adjust the suitable target effect concentration for each patient, based on the monitored physiological signals. To overcome this uncertainty, adaptive and predictive control strategies have been implemented to guarantee the regulation of the closed-loop system subject to positivity constraints (on the drug dose dosage), Chellaboina et al. (2006), Ionescu et al. (2008). Similar to what was done with the control of the NMB, a PID controller was developed to compute an individualized hypnotic propofol dose where the controller parameters were re-tuned based on the induced patient's response, Soltesz et al. (2011). The aforementioned controllers were meant for the automatic administration of the hypnotic propofol; however as it was mentioned in Mendonça et al. (2006) and Labbaf et al. (2010) that the opioid remifentanyl has influence in the DoA. Focused on this influence, closed-loop controllers were presented in Liu et al. (2011), Nogueira et al. (2014) to determine the amount of the two drugs that should be administered to the patient in a combined way to achieve a desired BIS.

Alternative control schemes adopting optimal control techniques have been widely used in the last years. The goal of optimal control is to find a control law for a given system such that a certain optimality criterion (for instance, the minimization of a certain cost function) is achieved.

An optimal control problem (OCP) usually involves a cost functional that is a function of the state and the control variables. The optimal control solution has to satisfy the system dynamic equations and to optimize the cost functional. Moreover, an OCP in general involves static constraints on the state and/or the control variables. The optimal control strategy can be derived using Pontryagin's Principle, Ross (2009), or by solving the Hamilton–Jacobi–Bellman equation, Bellman (1957). However, determining the analytical optimal solution can be difficult or even impossible to achieve. To overcome this issue, appropriate numeric solvers are used, see *e.g.* Paiva (2013). In Almeida et al. (2017), Almeida et al. (2015a) and Almeida et al. (2015b), optimal control theory was used to solve the problem of tracking a desired NMB or BIS level. This has the advantage of enabling a penalty for the excessive use of drug. The corresponding OCPs involve non-negativity constraints on the input and the state components, and are therefore hard to solve. Goebel and Subbotin (2007) propose a technique based on duality for Linear Quadratic Regulator (LQR) problems with constrained input, but assume that the origin is in the interior of the allowable set for the control inputs, which is not the case for the NMB and BIS control systems. In Beauchier and Winkin (2010) LQ optimal control of positive linear systems is studied. The optimal control is obtained through the solution of a Hamiltonian two point boundary value problem and it is time dependent, *i.e.*, it is an open-loop rather than a closed-loop (state feedback) solution. Furthermore, for the continuous time example presented in the paper the solution has to be obtained by numerical integration of the equations. A more recent paper on constrained LQR problems, Burachik et al. (2014), proposes to solve the dual of the LQR problem but yields again a controller that is time dependent and must be computed by a numerical algorithm. An alternative technique for the control of positive linear systems yielding a state feedback controller is derived in Roszak and Davison (2008), where a clamping controller with an integral term of the tracking error is proposed. Although this is an extremely interesting technique leading to a state feedback solution for positive linear systems, it does not correspond to the solution of an optimal control problem. Furthermore, the integral term may suffer from the well known phenomenon of windup, which should be avoided specially in the case of drug delivery, Almeida et al. (2017).

This thesis focuses on the feedback control of positive linear systems with a static nonlinearity at the output in the context of anesthesia. The controllers presented in this thesis were design based on simplified models, and consequently, present a simplified structure. More concretely, these controllers only depend on the parameters associated to the static nonlinear part of the model. A control law for positive systems is designed based on these simplified models and then compared with controllers obtained by solving an optimal control problem.

The manuscript is organized as follows. Chapter 2 presents a brief overview of compartmental systems together with the original and the simplified models used to design the control approaches. The identification method used here, the Extended Kalman Filter, is presented in Chapter 3. In Chapter 4 it is shown how the positive control law is designed for the NMB level and for the BIS level and the corresponding simulation results are shown. Chapter 5 presents the design of the state-feedback control using an optimal control problem formulated for the reference tracking of the NMB level and of the BIS level, respectively. Some brief conclusions are drawn in Chapter 6.

1.3 Thesis contributions

This thesis aims at giving further contributions to develop control schemes for drug administration during general anesthesia. In this context two important components of anesthesia are considered: the neuromuscular blockade (NMB) and the depth of anesthesia (DoA). The main contributions of this thesis are the following:

1. In the case of the control of NMB level, the reduced model proposed in 2012, Silva et al. (2012), involves two patient-dependent parameters, one in the linear part of the model and another one for the nonlinear part. Here, we propose a simplification of this model to design the controllers. More concretely, the control laws only have in consideration the parameter associated with the nonlinear model. In the case of the BIS level, the model proposed in Silva et al. (2014b) uses two patient-dependent parameters to describe the linear model and another two to describe the nonlinear model. For this case, the simplified model proposed here only takes into consideration the two patient-dependent parameters associated with the nonlinear model.
2. Design of two positive control laws based on the simplified models mention in 1 to control the NMB and the BIS level, respectively, as well as proof of the total system concentration convergence to desired values and subsequent guarantee of tracking of the desired NMB and BIS levels, respectively. The results obtained with these control laws are compared with the infusion drug administered by the anesthesiologist, manually.
3. Formulation of two optimal control problems for the control of the NMB and the BIS level. Due to the complexity associated with the existence of a positive constraint in the input the OCP is relaxed into a semi-definite program (SDP) by replacing the original variables by their moments up to a certain order. The optimal values of the moments are then computed by a semi-definite programming solver.
4. Comparison of the performance of the control techniques in simulated patients to analyze their incorporation in clinical environment, through the platform *Galeno*, Costa et al. (2014). The control approaches mentioned above are applied in different databases.

2

Compartmental models in anesthesia

In this chapter the models used to describe the relationship between the amount of administered drug and the corresponding physiological effect are presented. These models are naturally or artificially endowed with a compartmental structure. First, PK/PD models are introduced. Although they have a physiological meaning, they require a high number of patient-dependent parameters. Therefore we next present the reduced parameter models introduced in Silva et al. (2012), Silva et al. (2014b), which will be used in this thesis to design the control laws proposed in this thesis. Moreover, it is shown that these reduced models have an artificial compartmental structure which will be an important feature for the construction of controllers.

2.1 Compartmental models

Compartmental systems describe the transfer of matter between different compartments and play therefore an important role in modeling physiological processes. In this section a brief overview of such systems is presented.

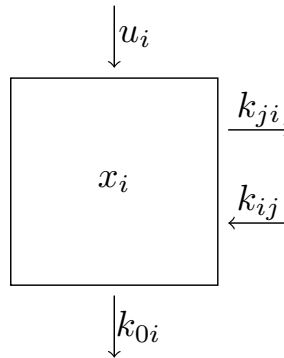


Figure 2.1: A compartment of a compartmental system.

In figure 2.1, x_i denotes the amount of relevant material in compartment i . The flow into compartment i from outside the system is denoted by u_i and is called *inflow*. Usually, u_i is a nonnegative function of time or just a nonnegative constant, but occasionally it may be dependent

on the compartment mass x as well. The constants $k_{ij} \geq 0$ and $k_{ji} \geq 0$ represent the proportional flows from compartment j into compartment i and from compartment i into compartment j , respectively. Finally, k_{0i} is the (proportional) *outflow* from compartment i to the environment. The mass balance equations for every compartment can be written as ordinary differential equations with the following form:

$$\dot{x}_i = \sum_{j \neq i}^n -k_{ji}x_i + k_{ij}x_j + u_i - k_{0i}x_i \quad (2.1)$$

Considering the equation (2.1) for all compartments one obtains a state-space model as in equation (2.2), which is a compartmental model in the sense of the following definition.

Definition 2.1 Linear compartmental system

A linear state-space system,

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t), \\ y(t) = Cx(t) + Du(t) \end{cases} \quad (2.2)$$

where $x(t) \in \mathbb{R}^{n \times 1}$ is the state vector, $u(t) \in \mathbb{R}^{p \times 1}$ is the input signal, $y(t) \in \mathbb{R}^{q \times 1}$ is the output, and $A \in \mathbb{R}^{n \times n}$, $B = (b_{ij}) \in \mathbb{R}^{n \times p}$, $C = (c_{lj}) \in \mathbb{R}^{q \times n}$ and $D = (d_{lj}) \in \mathbb{R}^{q \times p}$ with $n, p, q \in \mathbb{N}$ are the matrices of the system, is called **compartmental** if $A \in \mathbb{R}^{n \times n}$ is a compartmental matrix (see Definition 2.2 below) and moreover:

$$b_{ij} \geq 0 \quad \text{and} \quad c_{lj} \geq 0 \quad \forall i = 1, \dots, n; j = 1, \dots, p; l = 1, \dots, q.$$

Definition 2.2 Compartmental matrix

The matrix $A = (a_{ij}) \in \mathbb{R}^{n \times n}$ is a compartmental matrix if:

1. A is a matrix with nonnegative off-diagonal entries, i.e., A is a Metzler matrix:

$$a_{ij} \geq 0, \quad \forall i, j \in \{1, \dots, n\} \text{ and } i \neq j$$

2. A is a matrix with nonpositive diagonal entries:

$$a_{ii} \leq 0, \quad \forall i \in \{1, \dots, n\}$$

3. A is diagonally dominant:

$$|a_{ii}| \geq \sum_{j \neq i} a_{ji}, \quad \forall i \in \{1, \dots, n\}$$

Compartmental systems are a special class of positive systems. Therefore the state and output components are nonnegative provided that the initial state and the inputs are nonnegative.

Due to the high importance of compartmental models in the modeling of drug effects and to the good performance of controllers based on these models, they will be the basis for the work developed in this thesis.

The models presented in the next sections either possess by nature a compartmental structure or can be "artificially" endowed with such a structure. This will become clear in the sequel.

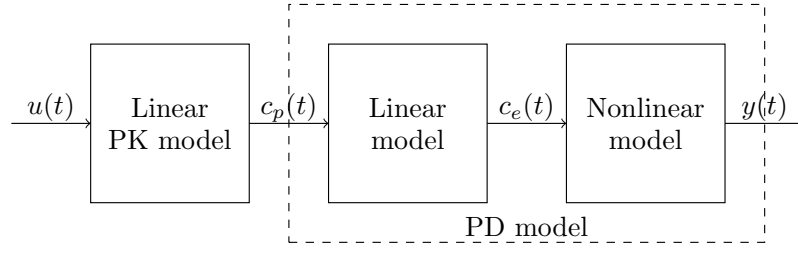


Figure 2.2: Block diagram for the Wiener PK/PD model.

2.2 PK/PD compartmental based models for drug effect

This section presents the standard models used to characterize the dynamic effect of drugs administered by continuous infusion on measured physiological variables, Meibohm and Derendorf (1997). These models rely on the knowledge about mass transfer between compartments in the human body and on the weights and volumes of such compartments. First, a linear pharmacokinetic (PK) model is used in order to explain the dynamic distribution of the administered drug dose, $u(t)$, through the different body compartments; this relates the model input $u(t)$ in Figure 2.2 (administered drug dose) with the drug concentration in the blood $c_p(t)$. Then, a set of two other blocks are connected in series with the first one, standing for the pharmacodynamics (PD), *i.e.*, in order to describe the relation between the plasmatic concentration, c_p , and the drug effect, y . More concretely, a linear differential equation relates the drug blood concentration $c_p(t)$ with its effect concentration $c_e(t)$ while a nonlinear static equation, known as the Hill equation, relates the effect concentration with the measured effect $y(t)$. This PK/PD structure for the effect of infused drugs constitutes a Wiener model: a linear dynamic part followed by a static nonlinear function, Wigren (1993).

As already mentioned, the dynamic blocks are based on physiological mechanisms that are well explained through compartmental models Godfrey (1983). The next sections present the PK/PD compartmental based models for the NMB and BIS cases.

2.2.1 Model for *atracurium* - NMB case

Due to the physiological meaning of the PK/PD compartmental based model, the number of compartments varies according to the place in the human body where the drug is eliminated. For instance, the model for the muscle relaxant *atracurium* only has three compartments because the drug is spontaneously degraded whereas the model for the muscle relaxant *rocuronium* has four compartments because the elimination of this drug is made by the liver, which corresponds to a new compartment.

Figure 2.3 shows the PK/PD compartmental model that relates the administered dose of *atracurium* with the effect concentration (corresponding to the first two blocks of the diagram in Figure 2.2). The state-space model that translates the exchange of the concentration of mass between the compartments is:

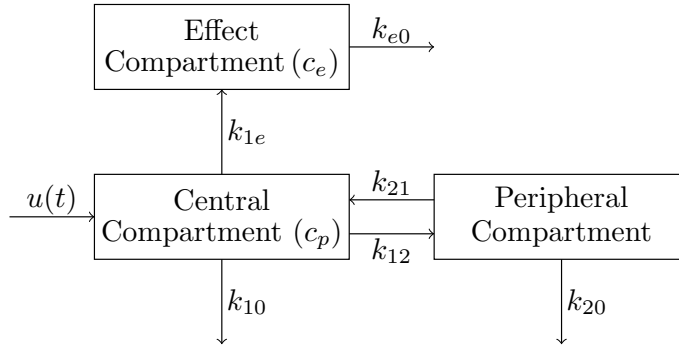


Figure 2.3: PK/PD compartmental model for the muscle relaxant *atracurium*. The central compartment is composed by the main organs heart, liver, lungs, kidney and by the blood, and the peripheral compartment corresponds, for instance, to the fat tissue and the cerebrospinal fluid. In this case the effect compartment corresponds to the muscle tissue.

$$\begin{aligned} \dot{x}(t) &= \begin{bmatrix} -(k_{12} + k_{10} + k_{1e}) & k_{21} \frac{V_2}{V_1} & 0 \\ k_{12} \frac{V_1}{V_2} & -(k_{21} + k_{20}) & 0 \\ k_{1e} \frac{V_1}{V_3} & 0 & -k_{e0} \end{bmatrix} x(t) + \begin{bmatrix} \frac{1}{V_1} \\ 0 \\ 0 \end{bmatrix} u(t) \\ c_e(t) &= \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} x(t) \end{aligned} \quad (2.3)$$

where $x(t) = [x_1(t) \ x_2(t) \ x_3(t)]^T$ is the time-varying mass concentration in each compartment, $u(t)$ is the infused drug dose and the constants k_{10} , k_{12} , k_{1e} , k_{e0} , k_{20} , k_{21} , which are patient dependent parameters, represent the proportional flows among the compartments and the flows from the compartments to the environment. V_1 , V_2 and V_3 correspond to the volumes of central compartment, of the peripheral compartment, and of the effect compartment, respectively.

As already mentioned the effect concentration, $c_e(t)$, is related with the measured effect, $y_{NMB}^{PK/PD}(t)$, through the Hill equation,

$$y_{NMB}^{PK/PD}(t) = \frac{100}{1 + \left(\frac{c_e(t)}{C_{50}} \right)^\gamma}, \quad (2.4)$$

where C_{50} and γ are patient dependent parameters, Weatherley et al. (1983).

Figure 2.4 shows the impulse effect concentration response (upper plot) and the impulse NMB level response (bottom plot) to an initial *bolus* of $500 \mu\text{g.kg}^{-1}$ of the simulated patient number 98, which has the following parameter values: $k_{10} = 0.1343 \text{ min}^{-1}$, $k_{12} = 0.2337 \text{ min}^{-1}$, $k_{1e} = 0.0028 \text{ min}^{-1}$, $k_{20} = 0$, $k_{21} = 0.1296 \text{ min}^{-1}$, $k_{e0} = 0.1064 \text{ min}^{-1}$, $C_{50} = 0.6900 \mu\text{g.ml}^{-1}$, $\gamma = 3.4982$. The set of the PK/PD parameters are presented in Appendix A.

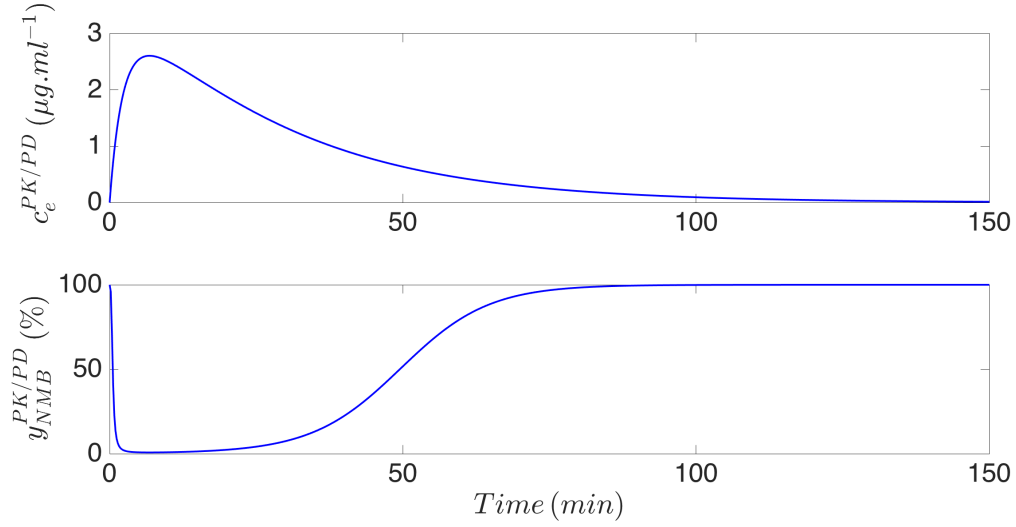


Figure 2.4: Impulse effect concentration (upper plot) and the impulse NMB level (bottom plot) to an initial *bolus* of $500\mu\text{g.kg}^{-1}$ of the muscle relaxant *atracurium* for the simulated patient number 98.

2.2.2 Model for *remifentanil* and *propofol* - BIS case

Similarly, to the muscle relaxant *rocuronium*, the hypnotic *propofol* and the analgesic *remifentanil* are degraded in the liver, and consequently, their PK/PD compartmental model has four compartments, Minto et al. (1997), Gepts et al. (1987). As it is possible to see in Figure 2.5, the drug is administered in the main compartment with an infusion rate $u(t)$ and the constants k_{e0} , k_{10} , k_{12} , k_{13} , k_{21} , k_{31} are the proportional flows among the compartments and the flows from the compartments to the environment. These constants depend on the considering drug, and also vary from patient to patient.

For each drug (*propofol* and *remifentanil*), the dynamic system that describes the exchange of the mass concentration between the compartments is represented by a state-space model with the following structure:

$$\begin{aligned} \dot{x}(t) &= \begin{bmatrix} -(k_{10} + k_{12} + k_{13}) & k_{21} \frac{V_2}{V_1} & k_{31} \frac{V_3}{V_1} & 0 \\ k_{12} \frac{V_1}{V_2} & -k_{21} & 0 & 0 \\ k_{13} \frac{V_1}{V_3} & 0 & -k_{31} & 0 \\ 0 & 0 & 0 & -k_{e0} \end{bmatrix} x(t) + \begin{bmatrix} \frac{1}{V_1} \\ 0 \\ 0 \\ 0 \end{bmatrix} u(t) \\ c_e(t) &= \begin{bmatrix} 0 & 0 & 0 & 1 \end{bmatrix} x(t) \end{aligned} \quad (2.5)$$

where V_i (ml) represents the volume of the compartment i . Here, compartments 1, 2 and 3 correspond to the central compartment, the peripheral compartment, and the effect compartment. In clinical practice, the anesthesiologists use population models to infer the response of each patient to a certain drug administration profile. For *propofol*, the parameters from Marsh's model, Marsh

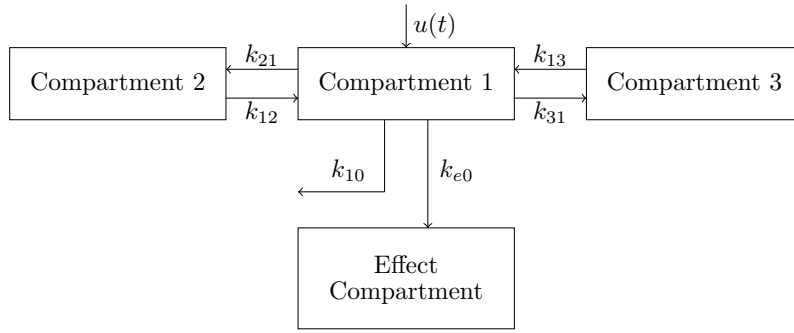


Figure 2.5: PK/PD compartmental based model for both *propofol* and *remifentanyl*.

et al. (1991), or from Schnider's model, Schnider et al. (1998), are usually used, whereas for *remifentanyl* the parameters from Minto's model, Minto et al. (1997) are used.

Both the *propofol* and the *remifentanyl* effect concentrations, $c_e^P(t)$ and $c_e^R(t)$, respectively, calculated from (D.1), are related with the measured effect, $y_{BIS}^{PK/PD}(t)$, by a nonlinear equation. First, $c_e^P(t)$ and $c_e^R(t)$ are normalized with respect to their concentration at half the maximal effect, C_{50}^P and C_{50}^R , respectively, as

$$U^P(t) = \frac{c_e^P(t)}{C_{50}^P}, \quad U^R(t) = \frac{c_e^R(t)}{C_{50}^R} \quad (2.6)$$

Due to the drug interaction, the joint effect of *propofol* and *remifentanyl* is a function of the potency of the drug mixture, which is defined as:

$$\phi = \frac{U^P(t)}{U^R(t) + U^P(t)}. \quad (2.7)$$

The joint drug effect is computed by a generalized Hill equation as

$$y(t)_{BIS}^{PK/PD} = y_0 \left(1 - \frac{\left(\frac{U^P(t) + U^R(t)}{U_{50}(\phi)} \right)^\gamma}{1 + \left(\frac{U^P(t) + U^R(t)}{U_{50}(\phi)} \right)^\gamma} \right), \quad (2.8)$$

where y_0 is the BIS level at zero concentration, γ is a patient parameter, and $U_{50}(\phi)$ is associated with the half of the maximum effect of both drugs at ratio ϕ and is determined as

$$U_{50}(\phi) = 1 - \beta\phi + \beta\phi^2, \quad (2.9)$$

where β is also a patient parameter.

Figure 2.6 shows the simulated BIS level response to a *bolus* (modeled as an impulse) of *propofol* combined with a *bolus* (impulse) of *remifentanyl*.

To simulate the impulse response for this PK/PD model, the parameters associated with the linear model for *propofol* were obtained by Schnider's model, whereas for *remifentanyl* the parameters were obtained by Minto's model (an explanation of how to obtain these parameter values is

given in the Appendix D). More concretely, the values used in the simulation of the linear part are the ones in Table 2.1.

Table 2.1: Values used to simulate the linear model of the PK/PD model both for *propofol* and for *remifentanyl*, corresponding to the Schnider model and the Minto model, respectively, for a 56 year-old female with 160cm of height and 88kg of weight.

	Propofol	Remifentanyl
$k_{10} (\text{min}^{-1})$	0.6083	0.5106
$k_{12} (\text{min}^{-1})$	0.2853	0.3585
$k_{13} (\text{min}^{-1})$	0.1958	0.0132
$k_{21} (\text{min}^{-1})$	0.0687	0.1981
$k_{31} (\text{min}^{-1})$	0.0035	0.0107
$k_{e0} (\text{min}^{-1})$	0.4590	0.4830
$V_1 (\text{ml})$	4.2700	4.3745
$V_2 (\text{ml})$	17.7270	7.9165
$V_3 (\text{ml})$	238	5.4200

The values associated with the nonlinear Hill equation are: $C_{50}^P = 13.9395(\text{mg.ml}^{-1})$, $C_{50}^R = 41.6474(\text{mg.ml}^{-1})$, $\beta = 3.3266$ and $\gamma = 2.0321$. These values were obtained using the hybrid method for parameter estimation presented in Mendonça et al. (2012).

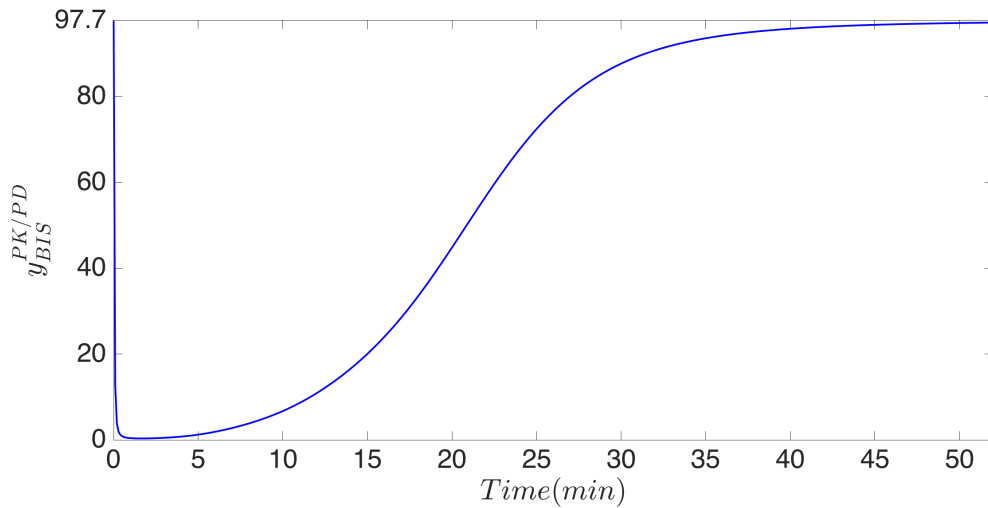


Figure 2.6: Simulated BIS level response to a *bolus* (modeled as an impulse) of *propofol* combined with a *bolus* (impulse) of *remifentanyl*.

2.3 Reduced parameter compartmental models for drug effect

This section presents compartmental models based on the reduced parameters models recently proposed by Silva et al. (2012), Silva et al. (2014b). To characterize the dynamic effect of drugs administered by continuous infusion on measured physiological variables. Similarly, to the PK/PD

compartmental based model, these models have a Wiener structure and they relate the model input $u(t)$ (administered drug dose) with a standardized effect concentration by means of a linear dynamics, while a nonlinear static equation relates the standardized effect concentration with the measured effect $y(t)$.

2.3.1 Model for *atracurium* - NMB case

In Silva et al. (2012) an alternative model was introduced to describe the relationship between the administered drug dose of the muscle relaxant, *atracurium*, and the measured effect, which in this case is the NMB level. This relationship is given by a SISO (*Single Input, Single Output*) Wiener model, as illustrated in Figure 2.7.

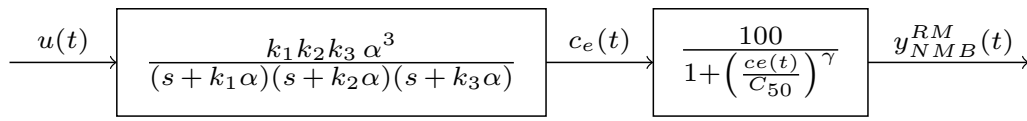


Figure 2.7: Block diagram that relates the drug dose of muscle relaxant, $u(t)$, with the NMB response, $y_{NMB}(t)$, according Silva et al. (2012).

The administered drug dose of the muscle relaxant is related with the standardized drug concentration in the effect compartment by the following third-order linear dynamical model:

$$C_e(s) = H(s)U(s), \quad (2.10)$$

with

$$H(s) = \frac{k_1 k_2 k_3 \alpha^3}{(s + k_1 \alpha)(s + k_2 \alpha)(s + k_3 \alpha)}, \quad (2.11)$$

and where $C_e(s)$ is the Laplace transform of the output of the linear of model, $c_e(t)$ ($\mu g. ml^{-1}$), that corresponds to the standardized effect concentration, and the $U(s)$ is the Laplace transform of the input signal, $u(t)$ ($\mu g. kg^{-1} . min^{-1}$), consisting of the muscular relaxant dose. Moreover, $k_1 < k_2 < k_3$ are positive constants which are fixed to be equal to 1, 4 and 10, respectively, and $\alpha > 0$ is a patient-dependent parameter.

Note that the transfer function $H(s)$ has three negative real poles namely, $s_1 = -k_1 \alpha$, $s_2 = -k_2 \alpha$ and $s_3 = -k_3 \alpha$, and is therefore BIBO (Bounded-Input, Bounded-Output) stable (see Definition 2.2.1. in Kisacanin and Agarwal (2001)).

Moreover, since $\lim_{s \rightarrow 0} H(s) = H(0) = \frac{k_1 k_2 k_3 \alpha^3}{k_1 \alpha k_2 \alpha k_3 \alpha} = 1$, the unit step response set point is given by $\lim_{s \rightarrow 0} s H(s) \frac{1}{s} = H(0) = 1$, see, *e.g.*, Bourlés (2013), meaning that, the transfer function $H(s)$ has unitary static gain. Note that the static gain of the linear part of the PK/PD model presented in Section 2.3.1 is in general not equal to 1. This explains why c_e is regarded as standardized effect concentration rather than an approximation of the actual effect concentration.

This new model replaces the linear part of the PK/PD model presented in Section 2.2.1 by means of the transfer function $H(s)$, which has a *parsimonious* structure, in the sense that the

patient's response is represented by a small number of parameters. More concretely, here there is only one patient-dependent parameter α instead of the six parameters of the linear PK/PD model. This model has great advantages from the point of view of parameter identification and implementation of online controllers.

The transfer function $H(s)$ can be realized by the following state-space model,

$$\begin{cases} \dot{x}(t) = \alpha A x(t) + \alpha B u(t) \\ c_e(t) = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} x(t) \end{cases}, \quad (2.12)$$

where $x(t) = \begin{bmatrix} x_1 & x_2 & x_3 \end{bmatrix}^T$ is the state vector and the matrices A and the vector B are defined as

$$A = \begin{bmatrix} -k_3 & 0 & 0 \\ k_2 & -k_2 & 0 \\ 0 & k_1 & -k_1 \end{bmatrix} \quad \text{and} \quad B = \begin{bmatrix} k_3 \\ 0 \\ 0 \end{bmatrix}.$$

Note that the state component $x_3(t)$ corresponds to the effect concentration. Although this model does not have a physiological meaning, it can be seen as a compartmental model similar to the one presented in Figure 2.3 (Section 2.2.1). Figure 2.8 shows this artificial compartmental structure.

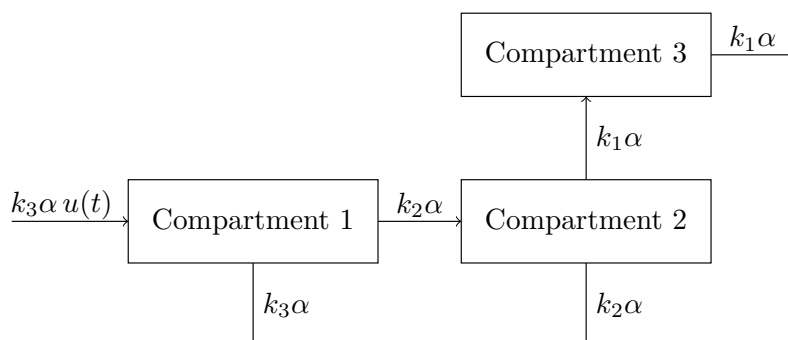


Figure 2.8: Diagram block that represents the artificial compartmental structure of the state-space realization (2.12) of the reduced model for the NMB response to *atracurium*.

As shown in Figure 2.7, the effect concentration is related with the patient NMB level through the following nonlinear static equation, known as Hill equation, Weatherley et al. (1983),

$$y_{NMB}^{RM}(t) = \frac{y_0}{1 + \left(\frac{c_e(t)}{C_{50}} \right)^\gamma}, \quad (2.13)$$

where C_{50} denotes the effect concentration at half of the maximal effect, and is taken to be fixed at the value 3.2435, y_0 is equal to the maximum value of y_{NMB} , which is 100% and γ is a patient-dependent parameter.

The overall model only has two parameters (α and γ) to be identified for each patient, in contrast with the eight of the PK/PD model presented in Section 2.2.1 and is therefore referred to as reduced model.

Figure 2.9 shows the impulse standardized effect concentration and the impulse NMB response to an initial *bolus* of $500\mu\text{g.kg}^{-1}$ of *atracurium* when the patient number 98 of the database is modeled by the reduced model. The patient parameters are: $\alpha = 0.0425$ and $\gamma = 4.020$. The set of the parameters for this model are presented in Appendix B.

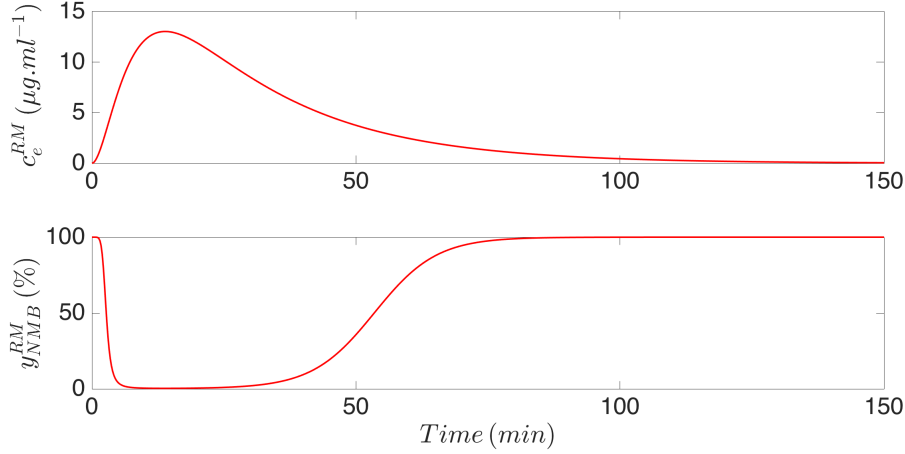


Figure 2.9: Impulse standardized effect concentration (upper plot) and impulse NMB response (bottom plot) to an initial *bolus* of $500\mu\text{g.kg}^{-1}$ of *atracurium* for the simulated patient number 98.

Figure 2.10 shows the comparison between the NMB response obtained by the two models for a patient simulated with the mean values of the parameters of the database. As it is possible to see, the reduced model approximates well the NMB response of the PK/PD model.

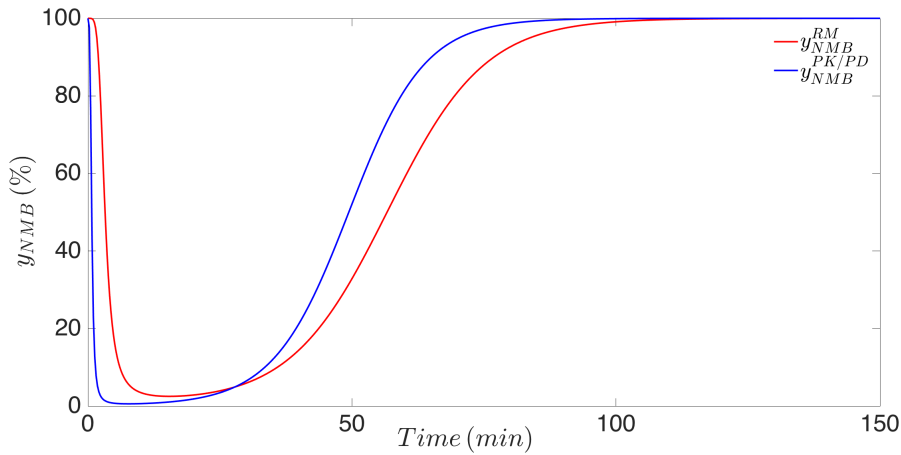


Figure 2.10: NMB impulse responses obtained through the reduced model (red line) and through the PK/PD model (blue line).

The complete reduced model is a good approximation to the PK/PD model. This together with other published results, Silva et al. (2014a), has motivated its use in this thesis for the construction of some automatic control schemes.

2.3.2 Model for *remifentanyl* and *propofol* - BIS case

Similar to the NMB case, a reduced Wiener model was proposed in Silva et al. (2014b) for the description of the joint effect of propofol and remifentanyl on the BIS level. This model consists of two linear parts, one for the relationship between the propofol dose and its standardized effect concentration and another one for the standardized effect concentration of remifentanyl, followed by static nonlinear equation, as shown in Figure 2.11.

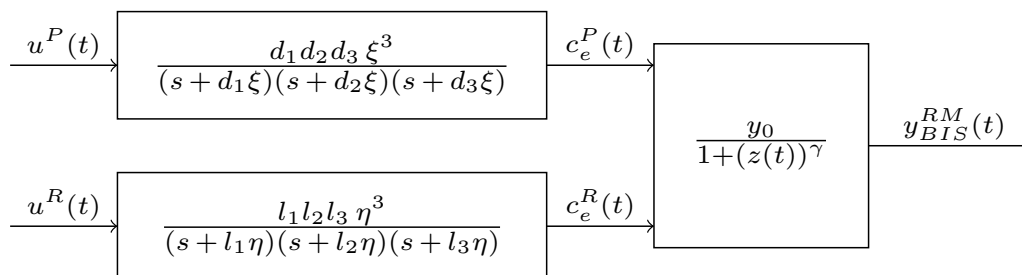


Figure 2.11: Block diagram that relates the drug doses of the propofol, $u^R(t)$, and remifentanyl, u^P , with the BIS level, $y_{BIS}(t)$, according to Silva et al. (2014b).

Each individual linear model is similar to the one presented in the previous section for the NMB level and has therefore the same properties.

The linear dynamics of the *propofol* model is given by the transfer function

$$H^P(s) = \frac{C_e^P(s)}{U^P(s)} = \frac{d_1 d_2 d_3 \xi^3}{(s + d_1 \xi)(s + d_2 \xi)(s + d_3 \xi)}, \quad (2.14)$$

and the linear model for the effect concentration of remifentanyl is similarly given by

$$H^R(s) = \frac{C_e^R(s)}{U^R(s)} = \frac{l_1 l_2 l_3 \eta^3}{(s + l_1 \eta)(s + l_2 \eta)(s + l_3 \eta)}, \quad (2.15)$$

where $C_e^P(s)$ and $C_e^R(s)$ are the Laplace transforms of the standardized effect concentrations of propofol and remifentanyl, $c_e^P(t)$ ($mg \cdot ml^{-1}$) and $c_e^R(t)$ ($mg \cdot ml^{-1}$), respectively; $U^P(s)$ and $U^R(s)$ are the Laplace transforms of the input doses of propofol and remifentanyl, $u^P(t)$ ($mg \cdot min^{-1}$) and $u^R(t)$ ($mg \cdot min^{-1}$), respectively.

Again, d_1, d_2, d_3 and l_1, l_2, l_3 have fixed values that have been suitably determined in Silva et al. (2014b); d_1, d_2, d_3 are equal to 1, 9 and 10, respectively, and l_1, l_2, l_3 are equal to 1, 2 and 3, respectively; ξ and η are the patient dependent parameters.

This reduced model replaces the linear part of the PK/PD model for both the hypnotic and the analgesic model through the transfer functions $H^P(s)$ and $H^R(s)$, respectively, with a minimal number of parameters to represent the patient's response.

A state-space representation for the linear part of the hypnotic model is given by:

$$\begin{cases} \dot{x}^P(t) = \xi A^P x^P(t) + \xi B^P u^P(t) \\ c_e^P(t) = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} x^P(t), \end{cases} \quad (2.16)$$

where the matrix A^P and the vector B^P are defined as

$$A^P = \begin{bmatrix} -d_3 & 0 & 0 \\ d_2 & -d_2 & 0 \\ 0 & d_1 & -d_1 \end{bmatrix} \quad \text{and} \quad B^P = \begin{bmatrix} d_3 \\ 0 \\ 0 \end{bmatrix}. \quad (2.17)$$

Similarly, a state-space representation for the linear part of the analgesic model is

$$\begin{cases} \dot{x}^R(t) = \eta A^R x^R(t) + \eta B^R u^R(t) \\ c_e^R(t) = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} x^R(t) \end{cases} \quad (2.18)$$

where the matrix A^R and the vector B^R are defined as

$$A^R = \begin{bmatrix} -l_3 & 0 & 0 \\ l_2 & -l_2 & 0 \\ 0 & l_1 & -l_1 \end{bmatrix} \quad \text{and} \quad B^R = \begin{bmatrix} l_3 \\ 0 \\ 0 \end{bmatrix}. \quad (2.19)$$

Similarly, to the NMB model, the reduced model for the depth of anesthesia does not have a physiological meaning and a natural compartmental structure; however it is possible represent it as two artificial compartmental models (one for *propofol* and another one for *remifentanyl*), where each one has a block diagram structure as depicted in Figure 2.8, with the obvious adaptations for the proportional flows values.

The nonlinear static equation proposed in Silva et al. (2014b) to describe the drug interaction and the relation between the effect concentration and the drug effect, the BIS level, is given by

$$y_{BIS}^{RM}(t) = \frac{y_0}{1 + z(t)\zeta}, \quad (2.20)$$

with $z(t) = mU^P(t) + U^R(t)$, $U^P(t) = \frac{c_e^P(t)}{C_{50}^P}$ and $U^R(t) = \frac{c_e^R(t)}{C_{50}^R}$; m and ζ are patient-dependent parameters and C_{50}^P and C_{50}^R have fixed values for all patients, namely 10 mg.ml^{-1} and 0.1 mg.ml^{-1} , respectively, y_0 is equal to 97.7 which corresponds to the maximum value of $y_{BIS}^{RM}(t)$. This can be viewed as a simplified Hill equation. Thus, the BIS model has as parameter vector $\theta = \begin{bmatrix} \xi & \eta & m & \zeta \end{bmatrix}^T$. Figure 2.12 shows the impulse response of the BIS level for patient 1 in the BIS database when *propofol* and *remifentanyl* are administered as hypnotic and analgesic, respectively, both for the PK/PD model and for the reduced model. The values of the parameters used to simulate this patient's response can be found in Appendix D and in Appendix E, respectively, and are equal to $V_1 = 4.27$, $V_2 = 17.73$, $V_3 = 238$, $k_{10} = 0.6081$, $k_{12} = 0.2853$,

$k_{13} = 0.196$, $k_{21} = 0.0687$, $k_{31} = 0.0035$ and $k_{e0} = 0.456$ for the *propofol* PK/PD model and are equal to $V_1 = 4.37$, $V_2 = 7.91$, $V_3 = 5.42$, $k_{10} = 0.5106$, $k_{12} = 0.3585$, $k_{13} = 0.0132$, $k_{21} = 0.1981$, $k_{31} = 0.0107$ and $k_{e0} = 0.483$, for the *remifentanyl* PK/PD model, and equal to $\xi = 0.0667$, $\eta = 0.3989$, $m = 2.1502$ and $\zeta = 1.7695$, for the reduced model.

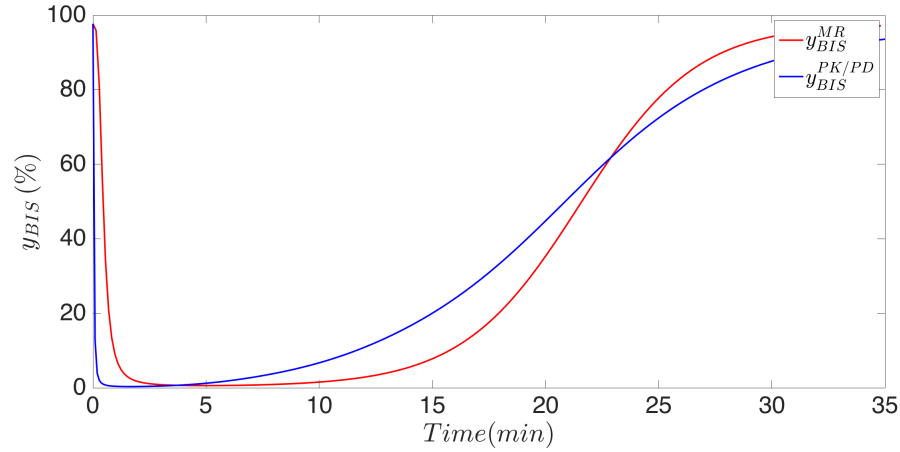


Figure 2.12: Impulse responses of the BIS level when *propofol* and *remifentanyl* are administered as hypnotic and analgesic, respectively, obtained with the reduced model (red line) and with the PK/PD model (blue line).

In this chapter, the definition of compartmental systems was introduced and it was proved that the reduced parameter models can be viewed as compartmental systems as they allow compartmental state space realizations. Furthermore, comparisons between the PK/PD models and the reduced parameter models, for the NMB and BIS level, were performed. The similarity of the impulse responses obtained for the two types of models justifies the used of the reduced parameter models in the controller design.

3

System Identification

This chapter presents the method used to identify the patient parameters, namely the Extended Kalman Filter. This method is applied to the NMB model and to the BIS model.

3.1 Introduction

In 1960, Rudolph E. Kalman published a paper, Kalman (1960), where a recursive method to obtain an estimate of the solution of a discrete-time linear system was proposed, which became known as the Kalman Filter (KF). With the inscrease of the digital computation, the Kalman filter has been widely used in system identification. This filter produces and estimate of the state of a system from a set of observations by minimizing the mean observed squared error, Welch and Bishop (1995).

The Extended Kalman Filter (EKF) is the version of the Kalman filter for nonlinear systems, but it can also be used to estimate model parameters by considering such parameters as extra state components. This will be explained in this thesis in order to identify the patient-dependent parameters for the NMB and BIS models.

Let us consider the following nonlinear discrete time system:

$$\begin{cases} x^d(k+1) &= f(k, x^d(k), u^d(k)) + g(k, x^d(k)) w(k) \\ y^d(k) &= h(k, x^d(k)) + e(k), \end{cases} \quad (3.1)$$

where $x^d(k) \in \mathbb{R}^{n \times 1}$ is the state vector, $u^d(k) \in \mathbb{R}^{p \times 1}$ the vector of inputs and $y^d(k) \in \mathbb{R}^{q \times 1}$ the vector of system output; $w(t)$ and $e(t)$ are the process noise and the observation noise, both of which are white and gaussian and have covariance matrices $R_1(t)$ and $R_2(t)$, respectively. The EKF allows an individualized adjustment of the states based on the evolution of the covariance matrices of the state estimate.

The algorithm of the EKF for continuous-time systems can be summarized in the following

equations, Söderström (2002):

$$\begin{aligned}
H(k) &= \left. \frac{\partial h(k, x^d)}{\partial x^d} \right|_{x^d = \hat{x}^d(k|k-1)} \\
K(k) &= P(k|k-1)H^T(k) \\
&\quad \times [H(k)P(k|k-1)H^T(k) + R_2(k)]^{-1} \\
\hat{x}^d(k|k) &= \hat{x}^d(k|k-1) + K(k)[y^d(k) - h(k, \hat{x}^d(k|k-1))] \\
P(k|k) &= P(k|k-1) - K(k)H(k)P(k|k-1) \\
\hat{x}^d(k+1|k) &= f(k, \hat{x}^d(k|k), u^d(k)) \\
F(k) &= \left. \frac{\partial f(k, x^d)}{\partial x^d} \right|_{x^d = \hat{x}^d(k|k)} \\
G(k) &= g(k, x^d)|_{x^d = \hat{x}^d(k|k)} \\
P(k+1|k) &= F(k)P(k|k)F^T(k) + G(k)R_1(k)G^T(k),
\end{aligned} \tag{3.2}$$

where $K(k)$ is the Kalman gain at the instant k , $\hat{x}^d(k|k)$ is the a priori state estimate, $P(k|k)$ is the corresponding covariance matrix, $\hat{x}^d(k+1|k)$ is the a posteriori state estimate and $P(k+1|k)$ is its covariance matrix.

The next two sections present the application of the EKF to the NMB model and to the BIS model in order to identify their patient-dependent parameters.

3.2 NMB model identification

In order to apply the EKF, the NMB model (2.12), with parameters α and γ , is first discretized using the *zero-order hold* (zoh) method, see, e.g., Chen (1998), yielding:

$$\begin{cases} x^d(k+1) &= \Phi(\alpha)x^d(k) + \Gamma(\alpha)u^d(k) \\ c_e^d(k) &= Cx^d(k), \end{cases} \tag{3.3}$$

where

$$\begin{cases} \Phi(\alpha) &= e^{A(\alpha)h} \\ \Gamma(\alpha) &= \int_0^h e^{A(\alpha)s} ds B(\alpha), \end{cases}$$

h is the (fixed) sampling time, for a given continuous time function $r(\cdot)$, $r^d(k) = r(kh)$, $k = 0, 1, 2, \dots$, $x^d \in \Re^{3 \times 1}$ is the discrete state, $c_e^d \in \Re$ is the output of the system (effect concentration of the drug) and the matrices $\Phi(\alpha) \in \Re^{3 \times 3}$ and $\Gamma(\alpha) \in \Re^{3 \times 1}$ are the counterparts of the matrices $A(\alpha)$ and $B(\alpha)$ in the discretized system. Note that, the zoh discretization method is only exact if the input is constant in each sampling interval, Chen (1998). In the NMB case, this sampling interval usually lasts 20 seconds.

As mentioned before, the static nonlinear part of the NMB model is described by the Hill equation,

$$y_{NMB}^d(k) = \frac{100}{1 + \left(\frac{c^d(k)}{C_{50}}\right)^\gamma} = \frac{100}{1 + \left(\frac{C_{x^d(k)}}{C_{50}}\right)^\gamma}. \quad (3.4)$$

In addition to the state identification, $x_1^d(k)$, $x_2^d(k)$ and $x_3^d(k)$, the EKF allows to identify the parameters of the model, α and γ , by introducing them as components of an extended state, defined as:

$$\bar{x}^d(k) = \begin{pmatrix} \bar{x}_1^d(k) \\ \bar{x}_2^d(k) \\ \bar{x}_3^d(k) \\ \bar{x}_4^d(k) \\ \bar{x}_5^d(k) \end{pmatrix} = \begin{pmatrix} x_1^d(k) \\ x_2^d(k) \\ x_3^d(k) \\ \alpha^d(k) \\ \gamma^d(k) \end{pmatrix}, \quad (3.5)$$

whereas the dynamics of the first three components is given by (3.3), the evolution of the last two components, corresponding to the parameters is given by:

$$\begin{cases} \alpha^d(k+1) = \alpha^d(k) \\ \gamma^d(k+1) = \gamma^d(k) \end{cases} \quad (3.6)$$

as the true values of the parameters are fixed.

The model for the extended state vector, obtained by combining (3.3), (3.5) and (3.6), is as follows:

$$\begin{aligned} \bar{x}^d(k+1) &= \begin{pmatrix} \Phi(\alpha^d(k)) & \underline{0}_{(3 \times 2)} \\ \underline{0}_{(2 \times 3)} & I_{(2 \times 2)} \end{pmatrix} \begin{pmatrix} x^d(k) \\ \alpha^d(k) \\ \gamma^d(k) \end{pmatrix} + \begin{pmatrix} \Gamma(\alpha^d(k)) \\ \underline{0}_{(2 \times 1)} \end{pmatrix} u^d(k) + \begin{pmatrix} w_x(k) \\ w_\alpha(k) \\ w_\gamma(k) \end{pmatrix} \\ &\equiv \begin{pmatrix} f_1(k, \bar{x}^d(k), u^d(k)) \\ f_2(k, \bar{x}^d(k), u^d(k)) \\ \vdots \\ f_5(k, \bar{x}^d(k), u^d(k)) \end{pmatrix} + w(k) \\ &\equiv f(k, \bar{x}^d(k), u^d(k)) + w(k) \end{aligned} \quad (3.7)$$

$$\begin{aligned} y_{NMB}^d(k) &= \frac{100}{1 + \left(\frac{\bar{C}_{x^d(k)}}{C_{50}}\right)^{\bar{x}_4^d(k)}} \\ &\equiv h(k, \bar{x}^d(k)) + e(k) \end{aligned} \quad (3.8)$$

$$\bar{C} = (C \ 0 \ 0). \quad (3.9)$$

In order to apply the EKF algorithm it is necessary to compute the Jacobian matrices F and H for the functions $f(k, \bar{x}^d, u^d)$ and $h(k, \bar{x}^d)$, respectively. Here F is computed analytically as:

$$F(k) = \begin{pmatrix} \frac{\partial f_1(k, \bar{x}^d(k), u^d(k))}{\partial \bar{x}_1^d(k)} & \frac{\partial f_1(k, \bar{x}^d(k), u^d(k))}{\partial \bar{x}_2^d(k)} & \cdots & \frac{\partial f_1(k, \bar{x}^d(k), u^d(k))}{\partial \bar{x}_5^d(k)} \\ \vdots & \vdots & & \vdots \\ \frac{\partial f_5(k, \bar{x}^d(k), u^d(k))}{\partial \bar{x}_1^d(k)} & \frac{\partial f_5(k, \bar{x}^d(k), u^d(k))}{\partial \bar{x}_2^d(k)} & \cdots & \frac{\partial f_5(k, \bar{x}^d(k), u^d(k))}{\partial \bar{x}_5^d(k)} \end{pmatrix}, \quad (3.10)$$

whereas the H is obtained numerically, similar to what was done in Silva et al. (2012), as:

$$\begin{aligned} H(k) &= \frac{\partial h(k, \bar{x}^d(k))}{\partial \bar{x}^d(k)} \\ &= \frac{h(k, \bar{x}^d(k) + \Delta \bar{x}^d(k)) - h(k, \bar{x}^d(k))}{\Delta \bar{x}^d(k)}, \end{aligned} \quad (3.11)$$

$\Delta \bar{x}^d(k)$ represents the step of differentiation. Here, the step $\Delta \bar{x}^d(k) = 1 \times 10^{-5}$ was chosen.

The initial guess of the vector $\hat{\bar{x}}^d(k|k-1)$ influences the velocity of the estimate convergence towards the right values of the parameters. Here, and according to the values chosen in Silva et al. (2012), the initial guess is taken to be:

$$\hat{\bar{x}}^d(0|-1) = (0.000 \quad 0.000 \quad 0.000 \quad 0.030 \quad 1.000)^T. \quad (3.12)$$

The initial guess for the covariance matrix $P(k|k-1)$ was based on an empirical analysis taking into account the used database, Silva et al. (2012):

$$P(0|-1) = \mathbf{diag} \left(10 \quad 10^0 \quad 10^{-1} \quad 10^{-3} \quad 10^{-2} \right). \quad (3.13)$$

In a similar way the covariance matrices R_1 e R_2 are obtained as

$$R_1 = \mathbf{diag} \left(10^{-1} \quad 10^{-1} \quad 10^{-1} \quad 10^{-6} \quad 10^{-3} \right) \quad (3.14)$$

$$R_2 = 10^{-1}. \quad (3.15)$$

To analyze the performance of the identification method, simulations were carried out using real NMB signals collected from patients submitted to general anesthesia. Figures 3.1 and 3.2 show the patient response and the model parameters, respectively, identified by the EKF when the previous initial state and matrices are used.

As it is possible to see in Figure 3.1, the estimated signal obtained by the EKF reflects the behavior of the real signal.

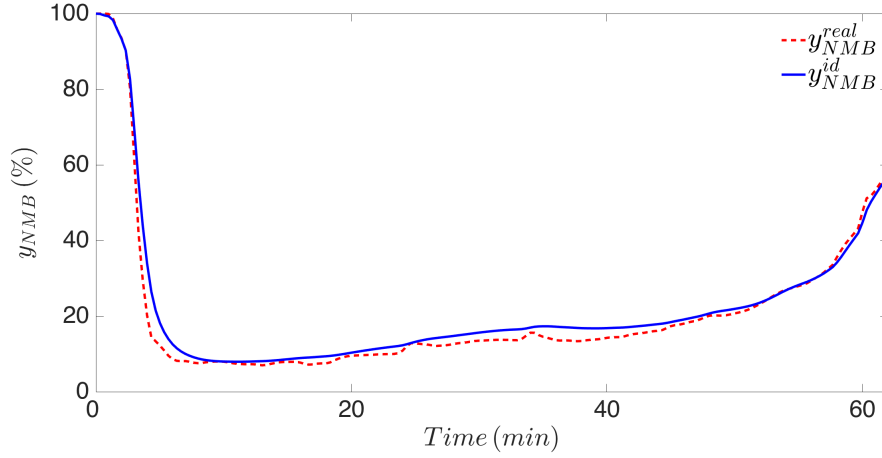


Figure 3.1: NMB level estimated by the EKF (blue line) and the one collected during a general anesthesia (red dashed line).

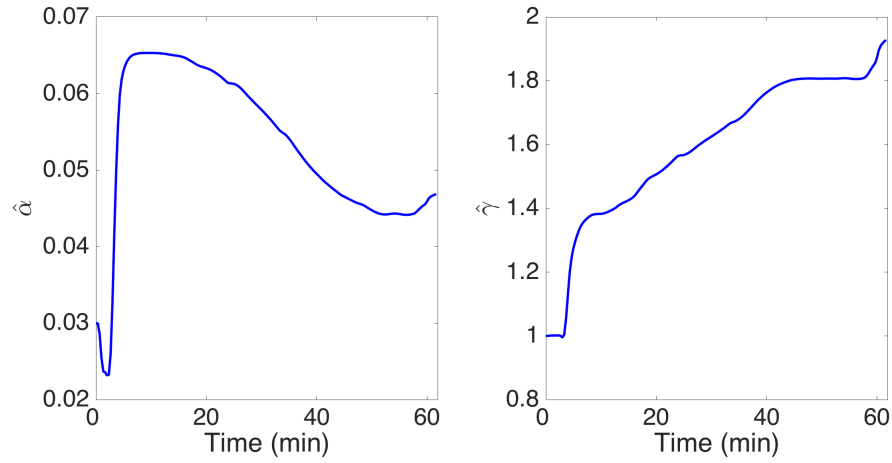


Figure 3.2: Parameter estimation performed by the EKF.

3.3 BIS model identification

Similarly to what was done to identify the parameters for the NMB model, this section presents the discrete time model used to apply the EKF for the identification of the parameters of the BIS model.

The discrete time BIS model for a sampling time h can be represented as follows.

$$\begin{cases} x^d(k+1) &= \Phi(\xi, \eta)x^d(k) + \Gamma(\xi, \eta)u^d(k) \\ z^d(k) &= C(m)x^d(k) \\ y_{BIS}^d(k) &= \frac{y_0}{1+(z^d(k))^\zeta}, \end{cases} \quad (3.16)$$

with

$$\begin{cases} \Phi(\xi, \eta) &= e^{A(\xi, \eta)h} \\ \Gamma(\xi, \eta) &= \int_0^h e^{A(\xi, \eta)s} ds B(\xi, \eta), \end{cases}$$

where the notation is similar to the one of the previous section. Moreover $u^d \in \mathfrak{R}^{2 \times 1}$ represents the drug dose infusion for *propofol* (first component) and *remifentanyl* (second component), $x^d \in \mathfrak{R}^{6 \times 1}$ is the discrete state, $z^d \in \mathfrak{R}$ is the joint effect concentration resulting from the interaction between *propofol* and *remifentanyl* and the matrices $\Phi(\xi, \eta) \in \mathfrak{R}^{6 \times 6}$ and $\Gamma(\xi, \eta) \in \mathfrak{R}^{6 \times 2}$ are the discrete counterparts of the matrices $A(\xi, \eta)$ and $B(\xi, \eta)$. The output of the model is y_{BIS}^d . Note that, for the BIS level, h is usually taken to be equal to 5 seconds.

As in the NMB model, in addition to the estimation of the state components, $x_1^d(k)$, $x_2^d(k)$, $x_3^d(k)$, $x_4^d(k)$, $x_5^d(k)$ and $x_6^d(k)$, the EKF is used to identify the parameters, ξ , η , m and ζ , of the model joining them to the state to obtain an extended state vector:

$$\bar{x}^d(k) = \begin{pmatrix} \bar{x}_1^d(k) \\ \bar{x}_2^d(k) \\ \vdots \\ \bar{x}_6^d(k) \\ \bar{x}_7^d(k) \\ \bar{x}_8^d(k) \\ \bar{x}_9^d(k) \\ \bar{x}_{10}^d(k) \end{pmatrix} = \begin{pmatrix} x_1^d(k) \\ x_2^d(k) \\ \vdots \\ x_6^d(k) \\ \xi^d(k) \\ \eta^d(k) \\ m^d(k) \\ \zeta^d(k) \end{pmatrix}, \quad (3.17)$$

The model for estimation of the extended state vector is obtained as in the NMB case, yielding:

$$\begin{aligned} \bar{x}^d(k+1) &= \begin{pmatrix} \Phi(\xi^d, \eta^d) & \mathbf{0}_{(6 \times 4)} \\ \mathbf{0}_{(4 \times 6)} & I_{(4 \times 4)} \end{pmatrix} \begin{pmatrix} x^d(k) \\ \theta^p(k) \end{pmatrix} + \begin{pmatrix} \Gamma(\xi^d, \eta^d) \\ \mathbf{0}_{(4 \times 2)} \end{pmatrix} u^d(k) + w(k) \\ &\equiv \begin{pmatrix} f_1(k, \bar{x}^d(k), u^d(k)) \\ f_2(k, \bar{x}^d(k), u^d(k)) \\ \vdots \\ f_{10}(k, \bar{x}^d(k), u^d(k)) \end{pmatrix} + w(k) \\ &\equiv f(k, \bar{x}^d(k), u^d(k)) + w(k) \end{aligned} \quad (3.18)$$

$$\begin{aligned} y_{BIS}^d(k) &= \frac{y_0}{1 + (\bar{C}(\theta) \bar{x}^d(k))^{\bar{x}_{10}^d(k)}} \\ &\equiv h(k, \bar{x}^d(k)) + e(k) \end{aligned} \quad (3.19)$$

$$\bar{C}(\theta) = \begin{pmatrix} C(\theta) & 0 & 0 & 0 & 0 \end{pmatrix}. \quad (3.20)$$

The linearization of the function $f(k, x)$ was performed analytically as,

$$F(k) = \begin{pmatrix} \frac{\partial f_1(k, \bar{x}^d(k), u^d(k))}{\partial \bar{x}_1^d(k)} & \frac{\partial f_1(k, \bar{x}^d(k), u^d(k))}{\partial \bar{x}_2^d(k)} & \cdots & \frac{\partial f_1(k, \bar{x}^d(k), u^d(k))}{\partial \bar{x}_{10}^d(k)} \\ \vdots & \vdots & & \vdots \\ \frac{\partial f_{10}(k, \bar{x}^d(k), u^d(k))}{\partial \bar{x}_1^d(k)} & \frac{\partial f_{10}(k, \bar{x}^d(k), u^d(k))}{\partial \bar{x}_2^d(k)} & \cdots & \frac{\partial f_{10}(k, \bar{x}^d(k), u^d(k))}{\partial \bar{x}_{10}^d(k)} \end{pmatrix} \quad (3.21)$$

and the linearization of the function $h(k, x^d)$ was performed numerically as in equation (3.12) with $\Delta \bar{x}^d(k) = 1 \times 10^{-13}$. The initial guess of the vector $\hat{\bar{x}}^d(k|k-1)$ corresponds to the minimal values for the states and for the parameters,

$$\hat{\bar{x}}^d(0|-1) = \begin{pmatrix} 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.1 & 0.1 & 2 & 1 \end{pmatrix}^T, \quad (3.22)$$

and the initial guess for the covariance matrix $P(k|k-1)$ was based on an empirical analyze taking into account the used database.

$$P(0|-1) = \mathbf{diag} \left(10^5 \quad 10^4 \quad 10 \quad 10^5 \quad 10^4 \quad 10 \quad 10^2 \quad 10^2 \quad 10^2 \quad 10^2 \right), \quad (3.23)$$

In a similar way the covariance matrices R_1 e R_2 are obtained as,

$$\begin{aligned} R_1 &= \mathbf{diag} \left(10^6 \quad 10^5 \quad 10^2 \quad 10^6 \quad 10^5 \quad 10^2 \quad 10^3 \quad 10^3 \quad 10^3 \quad 10^3 \right), \\ R_2 &= 1 \times 10^{13} \end{aligned} \quad (3.24)$$

To analyze the performance of the identification method, simulations were carried out using real BIS signals collect from patients submitted to general anesthesia when both *propofol* and *remifentanyl* were administered. More concretely, the response corresponds to the patient number 1 of the database presented in Appendix D. Figures 3.3 and 3.4, respectively, show the patient response and the model parameters, respectively, estimated by the EKF.

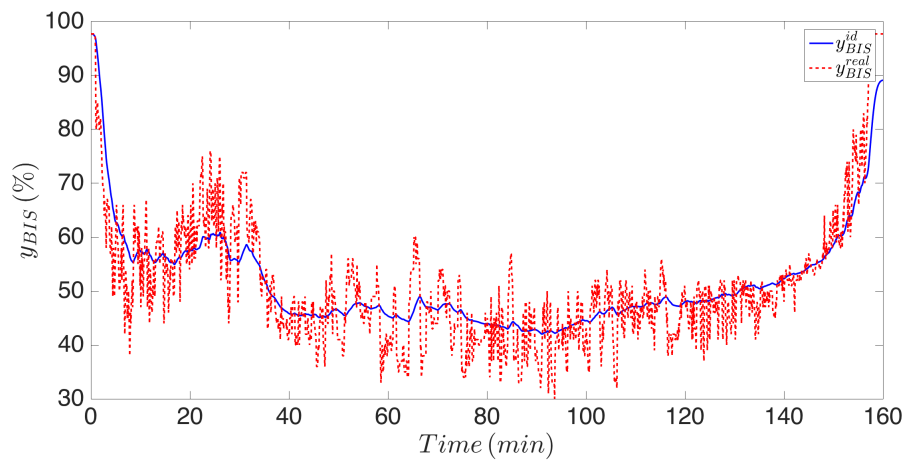


Figure 3.3: BIS level estimated by the EKF (blue line) and the one collected during a general anesthesia (red dashed line).

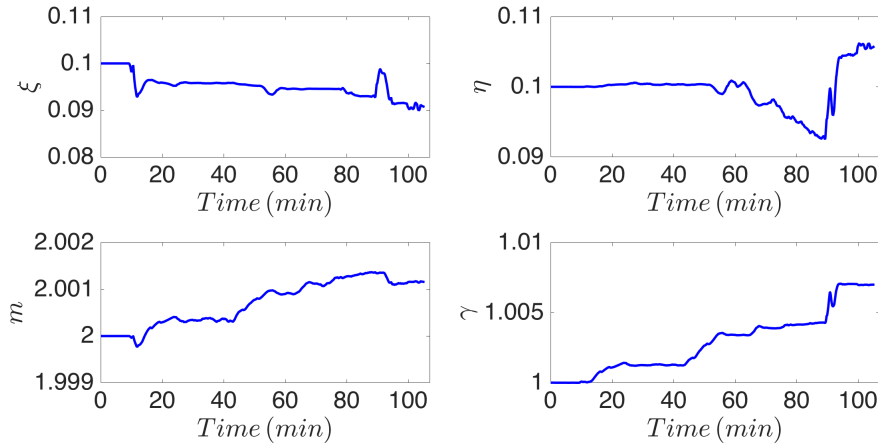


Figure 3.4: Parameter estimation performed by the EKF for the BIS model.

Figure 3.3 shows that the EKF estimates still capture the behavior of the BIS signal, even though the noise level is higher in this signal than in the NMB case. Due to the good results achieved with the EKF, in this thesis the model parameters needed for controller design will be identified using this method.

The results obtained in this section show that the response corresponding to the identified parameters reflects well the behavior of the real signal, even in the presence of a noise, as it is possible to see in the BIS case.

4

Simplified control applied in general anesthesia

In Bastin and Provost (2010) a positive control law for compartmental systems was proposed for the stabilization of the total system mass (*i.e.*, of the sum of the mass of the relevant material present in each system compartment). Although in the applications considered in this thesis concentrations, rather than masses, are used, a similar law can be applied to control the NMB level and the BIS level.

The original positive control law will be presented in this chapter for each model considered in Chapter 2. Moreover, a simplification of this law will be proposed to be applied in the administration of specific drugs during a general anesthesia. This simplified control scheme only requires the knowledge of half of the patient dependent parameters for the NMB model and for the BIS model.

At the end of the chapter, the control resulting from the combination of the simplified control law with the parameter identification is presented and applied to the databases for the NMB level and BIS level. The performance of the control scheme is analyzed using a cost functional that penalizes both the tracking error and the total amount of administered drug.

4.1 Positive control law

The control law presented in this section is the one introduced in Bastin and Provost (2010), originally designed as a positive control law for feedback stabilization of the total system mass in compartmental dynamical systems.

Recall the notion of compartmental system introduced in Def. 2.1

If x_i stands for the mass of the relevant material contained in compartment i , the total system mass, $M(x)$, for a system with n compartments is defined as:

$$M(x(t)) = \sum_{i=1}^n x_i(t) = \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} x(t). \quad (4.1)$$

The dynamics of $M(x(t))$ can be obtained from the compartmental system equations. Indeed, consider the following representation:

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t) \\ y(t) = Cx(t), \end{cases} \quad (4.2)$$

of a continuous single-input/single-output¹ compartmental system where $x(t) \in \mathbb{R}^n$ is the state vector, $u(t) \in \mathbb{R}$ is the input signal, and $A \in \mathbb{R}^{n \times n}$, $B \in \mathbb{R}^{n \times 1}$ and $C \in \mathbb{R}^{1 \times n}$ are the system matrices.

From the equation (4.1) and (4.2) we obtain:

$$\begin{aligned} \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} \dot{x}(t) &= \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} Ax(t) + \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} B\tilde{u}(t) \\ \Leftrightarrow \overbrace{M(x(t))}^{\dot{}} &= \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} Ax(t) + \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} B\tilde{u}(t), \end{aligned} \quad (4.3)$$

where $\overbrace{M(x(t))}^{\dot{}} = \frac{dM(x)}{dt}$.

In order to stabilize $M(x(t))$ at a given set point $M^* \geq 0$, the idea is to first determine $u(t) = \tilde{u}(t)$ such that,

$$\overbrace{M(x(t))}^{\dot{}} = -\lambda (M(x(t)) - M^*), \quad (4.4)$$

where λ is a positive arbitrary design parameter and M^* is the desired system mass. From equation (4.4) one obtains,

$$\overbrace{M(x(t))}^{\dot{}} = \overbrace{M(x(t)) - M^*}^{\dot{}} = -\lambda (M(x(t)) - M^*). \quad (4.5)$$

Setting $\Delta M = M(x(t)) - M^*$, equation (4.5) becomes,

$$\overbrace{\Delta M}^{\dot{}} = -\lambda \Delta M. \quad (4.6)$$

Since $-\lambda < 0$, the system (4.6) is asymptotically stable, *i.e.*,

$$\lim_{t \rightarrow +\infty} (M(x(t)) - M^*) = 0, \quad (4.7)$$

or, equivalently,

$$\lim_{t \rightarrow +\infty} M(x(t)) = M^*, \quad (4.8)$$

¹This is the case of interest for our application

Taking into account the equations (4.3) and (4.4):

$$\begin{bmatrix} 1 & \dots & 1 \end{bmatrix} Ax(t) + \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} B \tilde{u}(t) = -\lambda (M(x(t)) - M^*) \quad (4.9)$$

$$\begin{aligned} \Leftrightarrow \tilde{u}(t) &= \left(\sum_{i=1}^n b_i \right)^{-1} \left(-\lambda (M(x(t)) - M^*) - \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} Ax(t) \right) \\ \Leftrightarrow \tilde{u}(t) &= - \left(\sum_{i=1}^n b_i \right)^{-1} \left(\begin{bmatrix} 1 & \dots & 1 \end{bmatrix} Ax(t) + \lambda (M(x(t)) - M^*) \right), \end{aligned} \quad (4.10)$$

where b_i are the entries of the column matrix B of equation (4.2). In a second stage, in order to force its positivity, the input signal $u(t)$ is defined as:

$$u(t) = \max(0, \tilde{u}(t)) \quad (4.11)$$

The control law for the tracking of a desired reference level M^* for the total system mass is then given by:

$$\begin{cases} u(t) = \max(0, \tilde{u}(t)) \\ \tilde{u}(t) = - \left(\sum_{i=1}^n b_i \right)^{-1} \left(\begin{bmatrix} 1 & \dots & 1 \end{bmatrix} Ax(t) + \lambda (M(x(t)) - M^*) \right) \end{cases} \quad (4.12)$$

The following theorem guarantees the convergence of the state trajectories of the closed-loop system (4.2)-(4.12) to the set $\Omega_{M^*} = \{x \in \mathbb{R}^3 : M(x) = M^*\}$, known as the *iso-mass* corresponding to the value M^* .

Theorem 4.1.1 *For the closed-loop system (4.2)-(4.12) with arbitrary initial condition $x(0) \geq 0$ (i.e., with nonnegative components)*

- the *iso-mass* Ω_{M^*} is forward invariant;
- the state vector $x(t)$ is bounded for all $t > 0$ and converges to the *iso-mass* Ω_{M^*} .

The proof of this theorem is given in Almeida (2010).

The idea now is to use the mass control in order to achieve the control of a desired physiological effect. More concretely, it turns out that the control law (4.12) of a system (4.2) not only drives the system mass to a value M^* , but it also drives the system to a steady-state in the *iso-mass* Ω_{M^*} and consequently to a certain value of the output of the linear model (4.2), Almeida (2010). Therefore, by a suitable choice of the value M^* , one can obtain the desired steady-state value for $y(t)$, and consequently drive the desired physiological effect to a desired reference value.

4.1.1 Control for *atracurium* - NMB case

In this section the positive control law is applied to the NMB case to control the dose of muscle relaxant to be administered during a general anesthesia.

The control law is designed based on the reduced compartmental model presented in the previous chapter. Recall that, the effect concentration is obtained by the following state-space model

$$\begin{cases} \dot{x}(t) = \alpha \underbrace{\begin{bmatrix} -k_3 & 0 & 0 \\ k_2 & -k_2 & 0 \\ 0 & k_1 & -k_1 \end{bmatrix}}_A x(t) + \alpha \underbrace{\begin{bmatrix} k_3 \\ 0 \\ 0 \end{bmatrix}}_B u(t) \\ c_e(t) = \underbrace{\begin{bmatrix} 0 & 0 & 1 \end{bmatrix}}_C x(t), \end{cases} \quad (4.13)$$

with $k_1 = 1$, k_2 and $k_3 = 10$.

The neuromuscular blockade level is given by the Hill equation,

$$y_{NMB}(t) = \frac{100}{1 + \left(\frac{c_e(t)}{C_{50}} \right)^\gamma}. \quad (4.14)$$

The control law is obtained by substituting these matrices in the control law (4.12),

$$\begin{cases} u(t) = \max(0, \tilde{u}(t)) \\ \tilde{u}(t) = -\frac{1}{k_3} \left((k_2 - k_3)x_1(t) + (k_1 - k_2)x_2(t) - k_1x_3(t) \right) - \frac{1}{k_3\alpha} \lambda \left(M(x(t)) - M^* \right) \\ \tilde{u}(t) = -\frac{1}{10} \left(-6x_1(t) - 3x_2(t) - x_3(t) \right) - \frac{\lambda}{10\alpha} \left(M(x(t)) - M^* \right). \end{cases} \quad (4.15)$$

As mentioned before, a suitable choice of the value of M^* drives the desired NMB level to a desired reference value y_{NMB}^{ref} . For this purpose, the equilibrium point x^e of the closed-loop system (4.13)-(4.15) when $M(x(t)) = M^*$ is computed through the following system,

$$\begin{cases} \tilde{A}x^e(t) = 0 \\ M(x^e) = M^*. \end{cases} \quad (4.16)$$

where $\tilde{A} = A - \alpha \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} \begin{bmatrix} -6 & -3 & -1 \end{bmatrix}$ is the closed-loop matrix for $M(x) = M^*$, and consequently

$$u(t) = \tilde{u}(t) = -\frac{1}{10} \left(-6x_1(t) - 3x_2(t) - x_3(t) \right).$$

The obtained result is the vector,

$$x^e = \begin{bmatrix} \frac{M^*}{3} & \frac{M^*}{3} & \frac{M^*}{3} \end{bmatrix}. \quad (4.17)$$

Moreover, it can be shown that this equilibrium point is asymptotically stable with respect to the dynamics of the closed-loop system restricted to the iso-mass Ω_{M^*} , Almeida (2010). Therefore, setting

$$M^* = 3x_3^e = 3c_e^{ref}(\gamma), \quad (4.18)$$

where $c_e^{ref}(\gamma)$ is calculated by the inversion of the Hill equation (4.14),

$$c_e^{ref}(\gamma) = \left(\frac{100}{y_{NMB}^{ref}} - 1 \right)^{1/\gamma} C_{50}, \quad (4.19)$$

yields a control law that tracks the desired NMB reference level y_{NMB}^{ref} . This level is usually taken as 10% in the clinical practice for general anesthesia.

Figure 4.1 shows the NMB level evolution when the drug dose is determined by the controller presented above. As it is possible to see $M(x(t))$ converges to the desired system mass M^* and, consequently, the NMB level achieves the desired value of 10%. The controller was designed using the parameters of the model 17 of Appendix B. Using these parameters, $\alpha_{17} = 0.0366$, $\gamma_{17} = 1.9262$, and equations (4.18) and (4.19) the value of M^* is equal to $30.4458 \mu g \cdot ml^{-1}$. At the initial time, a typical *bolus* of $500 \mu g \cdot kg^{-1}$ of *atracurium* is administered and the controller actions begins after a certain time t^* . This instant time is computed by an algorithm proposed by Silva et al. (2009) called On Line tuned Algorithm for Recovery Detection (OLARD). This algorithm determines the instant when the patient begins to recover from the initial *bolus*. The design parameter λ was chosen empirically and taken equal to 0.2.

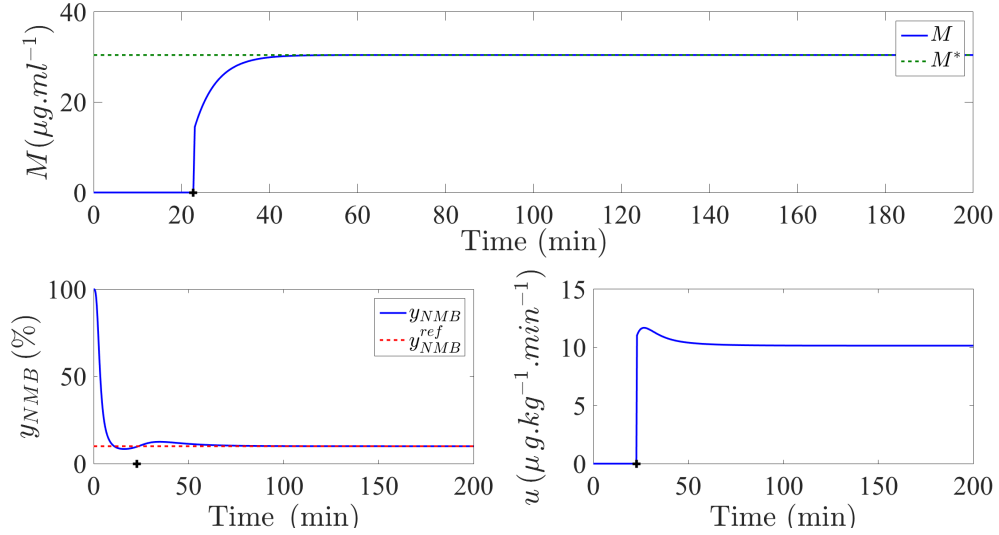


Figure 4.1: NMB level evolution when the drug dose is determined by the positive control law. The star represents the time instant when the controller action begins.

Figure 4.2 shows the NMB level for the hundred models presented in Appendix B and the average NMB level response for these cases, $\bar{y}_{NMB}$. As expected all cases achieve the desired NMB level despite the variability presented in the upper plot.

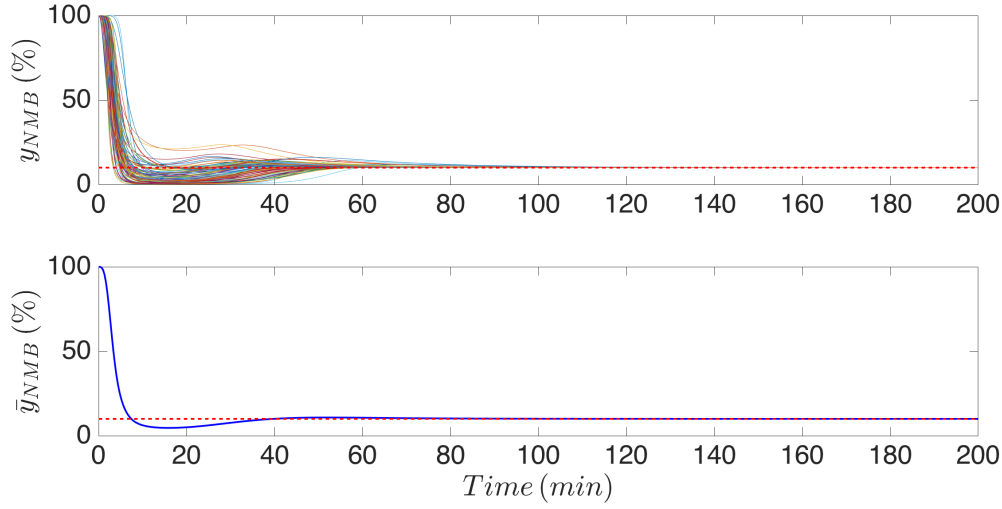


Figure 4.2: The upper plot presents the NMB level evolution when the drug dose is determined by the positive control law for the hundred models and the bottom plot presents the average response signal of these hundred models.

4.1.2 Control of *remifentanyl* and *propofol* - BIS case

In the same line of what has been done in the previous subsection, this section presents one control law for the hypnotic, *propofol*, and another one for the analgesic, *remifentanyl*, in order to achieve a desired BIS level. Since, the models are very similar, the control laws will be similar too.

As shown in the previous chapter, the models for the effect concentration of *propofol* and of *remifentanyl* are represented by the following state-space realizations, respectively,

$$\begin{cases} \dot{x}^P(t) = \underbrace{\xi \begin{bmatrix} -d_3 & 0 & 0 \\ d_2 & -d_2 & 0 \\ 0 & d_1 & -d_1 \end{bmatrix}}_{A^P} x^P(t) + \underbrace{\xi \begin{bmatrix} d_3 \\ 0 \\ 0 \end{bmatrix}}_{B^P} u^P(t) \\ c_e^P(t) = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} x^P(t), \end{cases} \quad (4.20)$$

$$\begin{cases} \dot{x}^R(t) = \underbrace{\eta \begin{bmatrix} -l_3 & 0 & 0 \\ l_2 & -l_2 & 0 \\ 0 & l_1 & -l_1 \end{bmatrix}}_{A^R} x^R(t) + \underbrace{\eta \begin{bmatrix} l_3 \\ 0 \\ 0 \end{bmatrix}}_{B^R} u^R(t) \\ c_e^R(t) = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} x^R(t), \end{cases} \quad (4.21)$$

with $d_1 = 1$, $d_2 = 9$, $d_3 = 10$, $l_1 = 1$, $l_2 = 2$ and $l_3 = 3$.

The bispectral index is related with each effect concentrations, $c_e^P(t)$ and $c_e^R(t)$ by the Hill equation,

$$y_{BIS}(t) = \frac{97.7}{1 + z(t)\zeta}, \quad (4.22)$$

where $z(t) = m \frac{c_e^P(t)}{C_{50}^P} + \frac{c_e^R(t)}{C_{50}^R}$. Note that, C_{50}^P and C_{50}^R have fixed values, namely $C_{50}^P = 10 \text{ mg.ml}^{-1}$ and $C_{50}^R = 0.1 \text{ mg.ml}^{-1}$.

Substituting the model matrices in the control law (4.12), the following control laws for the *propofol* and *remifentanyl*, are obtained, respectively,

$$\begin{cases} u^P(t) = \max(0, \tilde{u}^P(t)) \\ \tilde{u}^P(t) = -\frac{1}{d_3} \left((d_2 - d_3)x_1^P(t) + (d_1 - d_2)x_2^P(t) - d_1x_3^P(t) \right) - \frac{1}{d_3\xi} \lambda^P \left(M(x^P(t)) - M^{*P} \right) \\ \tilde{u}^P(t) = -\frac{1}{10} \left(-x_1^P(t) - 8x_2^P(t) - x_3^P(t) \right) - \frac{1}{10\xi} \lambda^P \left(M(x^P(t)) - M^{*P} \right) \end{cases} \quad (4.23)$$

$$\begin{cases} u^R(t) = \max(0, \tilde{u}^R(t)) \\ \tilde{u}^R(t) = -\frac{1}{l_3} \left((l_2 - l_3)x_1^R(t) + (l_1 - l_2)x_2^R(t) - l_1x_3^R(t) \right) - \frac{1}{l_3\eta} \lambda^R \left(M(x^R(t)) - M^{*R} \right) \\ \tilde{u}^R(t) = -\frac{1}{3} \left(-x_1^R(t) - x_2^R(t) - x_3^R(t) \right) - \frac{1}{10\eta} \lambda^R \left(M(x^R(t)) - M^{*R} \right) \end{cases} \quad (4.24)$$

A suitable choice of the values for the desired masses, M^{*P} and M^{*R} , drives the BIS level to a desired value. In the same line of what was done for the NMB level, to compute these values, the equilibrium points of the closed-loop system, when $M(x) = M^*$ were determined and the steady-state effect concentrations c_e^P and c_e^R were shown to be equal to $M^{*P}/3$ and $M^{*R}/3$, respectively, as in Nogueira et al. (2014). This enables to determine the value of M^{*P} and M^{*R} by the inversion of the Hill equation (4.14) for a desired steady-state value y_{BIS}^{ref} for the BIS level.

Indeed, on the one hand, we have

$$z^{ref} = \left(\frac{97.7}{y_{BIS}^{ref}} - 1 \right)^{1/\zeta}, \quad (4.25)$$

and on the other hand,

$$z^{ref} = m \frac{(c_e^P)^{ref}}{C_{50}^P} + \frac{(c_e^R)^{ref}}{C_{50}^R}. \quad (4.26)$$

Thus, once the patient dependent parameters ζ and m are known, a value of z^{ref} is obtained from (4.25) that can be replaced in (4.26). This still leaves a degree of freedom to in the determination of M^{*P} and M^{*R} from equation (4.26). To eliminate this degree of freedom, we assume that $M^{*P} = \rho M^{*R}$, for a fixed $\rho \geq 0$. Using this assumption and equation (4.26) we obtain the desired

system masses as,

$$\begin{aligned} M^{*P} &= \frac{3\rho z^{ref}}{\frac{1}{C_{50}^P} m\rho + \frac{1}{C_{50}^R}} \\ M^{*R} &= \frac{3z^{ref}}{\frac{1}{C_{50}^P} m\rho + \frac{1}{C_{50}^R}}. \end{aligned} \quad (4.27)$$

Note that, in steady-state, the proportion $\frac{M^{*P}}{M^{*R}} = \rho$ implies $\frac{u^P}{u^R} = \rho$.

Figures 4.3 and 4.4 show the performance of the positive control laws designed with the parameters of the patient number 18 of the database presented in Appendix E, $\xi_{18} = 0.1336$, $\eta_{18} = 0.2307$, $m_{18} = 1.2061$ and $\zeta_{18} = 1.0846$. The design parameters λ^P and λ^R were both chosen be equal to 1 and the proportion between the *propofol* dose and *remifentanyl* dose, ρ , was chosen be equal to 400 based on the proportion of the real doses administered during general anesthesia; the desired BIS level was set at 50%. As one can see in Figure 4.3, the system mass for both the *propofol* model and *remifentanyl* models $M^P(x^P(t))$ and $M^R(x^R(t))$ converge to the desired values, $M^{*P} = 19.7276 \text{ mg.ml}^{-1}$ and $M^{*R} = 0.0493 \text{ mg.ml}^{-1}$, respectively, and therefore the BIS level reaches the BIS reference level of 50%. This reference was chosen based on the adequate range values for the BIS level of a general anesthesia, which is between 40% and 60%. For

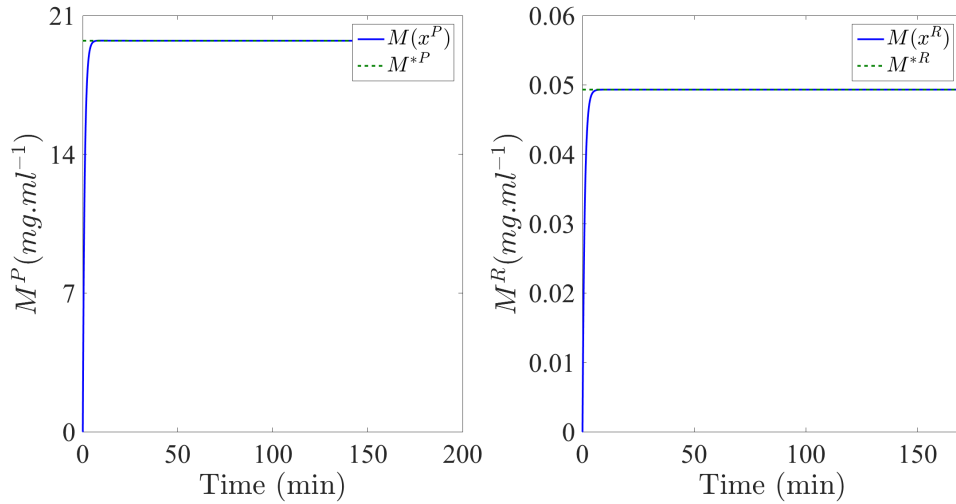


Figure 4.3: System mass evolution for the *propofol* model and for the *remifentanyl* model.

overall assessment, Figure 4.5 illustrates the BIS level of the eighteen cases presented in Appendix E when the control law for the *propofol* is given by (4.23) and the control law for *remifentanyl* by (4.24). The bottom plot represents the average BIS level response of the eighteen cases presented in the upper plot and as expected the BIS level reaches the target value of 50%.

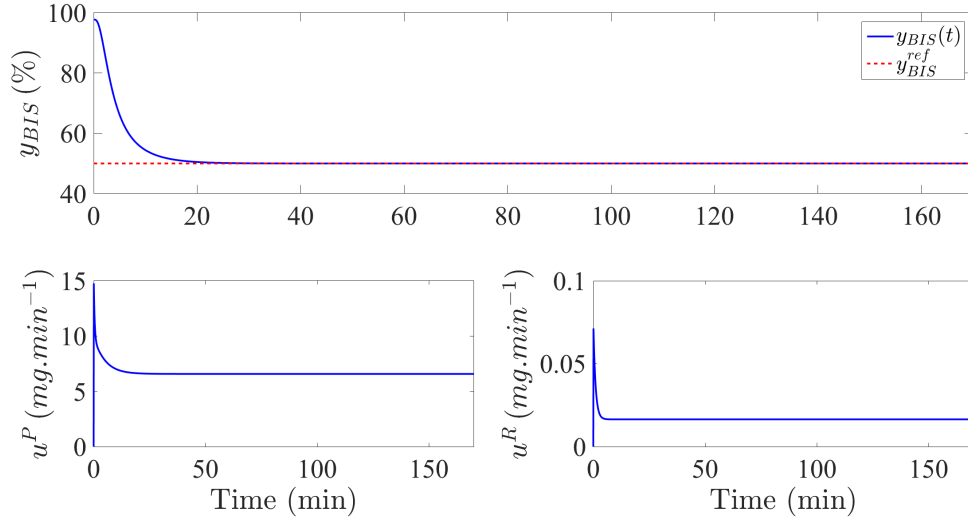


Figure 4.4: BIS level evolution when the drug doses of *propofol* and *remifentanyl* are determined by the positive control laws.

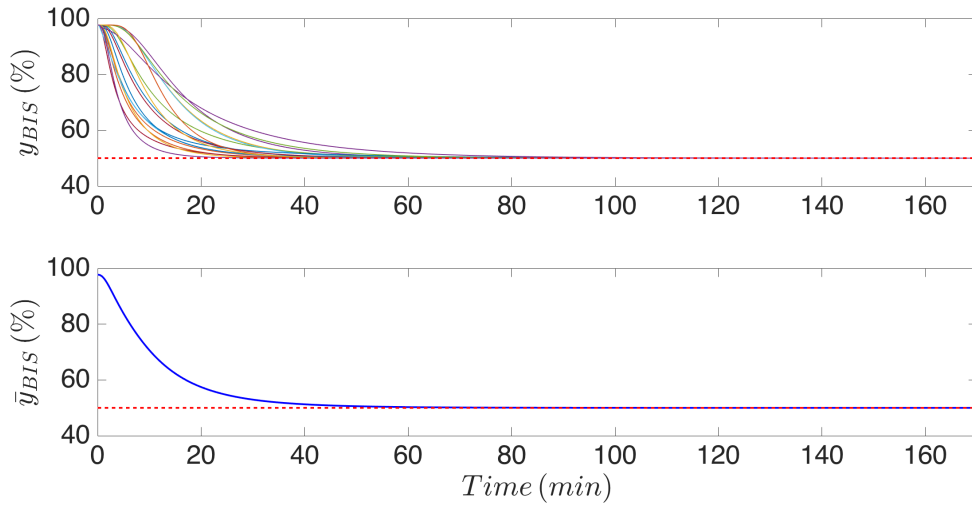


Figure 4.5: BIS level evolution when the drug doses of *propofol* and *remifentanyl* are determined by the positive control laws for the eighteen cases of Appendix E (upper plot) and the average of these eighteen signals (bottom plot). The dashed line represents the reference BIS level.

4.2 Simplified positive control law

In this section it is shown that the previously considered positive control law can be simplified. More concretely, the parameters associated with the linear models can be fixed and the controllers only depend on the parameters of the Hill equation. For this purpose, it is shown that the feedback stabilization of the $M(x)$ does not depend on the parameter θ , when the patient is modeled by a linear time-varying system with the following structure,

$$\dot{x}(t) = \theta Ax(t) + \theta Bu(t), \quad (4.28)$$

For a control law with a structure as,

$$\begin{cases} u(t) = \max(0, \tilde{u}(t)) \\ \tilde{u}(t) = - \left(\sum_{i=1}^n b_i \right)^{-1} \left(\begin{bmatrix} 1 & \dots & 1 \end{bmatrix} Ax(t) + \lambda (M(x(t)) - M^*) \right), \end{cases} \quad (4.29)$$

the effect of the simplified control law, assuming $\tilde{u}(t) > 0, \forall t$, is evaluated by the dynamics of the system error mass $\dot{\Delta M}(x)$:

$$\begin{aligned} \dot{\Delta M}(x) &= \dot{M}(x) = \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} \dot{x}(t) \\ &= \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} \theta Ax + \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} \theta B \tilde{u}(t) \\ &= \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} \theta Ax + \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} \theta B \left(- \left(\sum_{i=1}^n b_i \right)^{-1} \begin{bmatrix} 1 & \dots & 1 \end{bmatrix} Ax \right. \\ &\quad \left. - \left(\sum_{i=1}^n b_i \right)^{-1} \lambda (M(x) - M^*) \right) \\ &= -\theta \lambda (M(x) - M^*) \\ &= -\lambda_\theta \Delta M(x) \end{aligned} \quad (4.30)$$

Thus, the patient parameter θ may indeed be left out of the control law. Although θ influences the speed of convergence, this can be compensated by the design parameter λ . As it can be seen in (4.30), the controller actions only depend on a suitable choice of the value for M^* .

The advantage of this simplified control law is the decrease of the number of parameters needed to identify on real time and consequently the decrease of the errors associated with the system identification. Furthermore, the effort of tuning the covariance matrices in the EKF algorithm also decreases.

In the following sections, new controllers were designed according this simplification.

4.2.1 Simplified control for *atracurium* - NMB case

For the control of the NMB level, the simplified control law stays,

$$\begin{cases} u(t) = \max(0, \tilde{u}(t)) \\ \tilde{u}(t) = -\frac{1}{k_3} \left((k_2 - k_3)x_1 + (k_1 - k_2)x_2 - k_1x_3 \right) - \frac{1}{k_3\bar{\alpha}} \lambda (M(x(t)) - M^*), \end{cases} \quad (4.31)$$

where $\bar{\alpha}$ corresponds to the mean value for the parameter α , computed from our database. The only parameter involved in the design of the positive control law is the parameter γ in the calcula-

tion of the desired value for M^* , which is determined by equation (4.32)

$$M^* = 3x_3^e = 3c_e^{ref}(\gamma) = \left(\frac{100}{y_{NMB}^{ref}} - 1 \right)^{1/\gamma} C_{50}. \quad (4.32)$$

In order to validate this approach, *i.e.*, the use of the mean, $\bar{\alpha}$, of the parameter α to design the controller, a real drug dose profile was administered to a simulated model presented in Appendix B, under the conditions of the following two scenarios:

- (1) The model is simulated with $\alpha = \alpha_i$ and $\gamma = \gamma_i$ ($i \in \{1, \dots, 100\}$);
- (2) The model is simulated with $\alpha = \bar{\alpha} = 0.0382$ and $\gamma = \gamma_i$ ($i \in \{1, \dots, 100\}$);

Figure 4.6 shows the comparison of the NMB level simulated for the model $i = 2$ ($\alpha_2 = 0.0412$ and $\gamma_2 = 2.9740$) when the real drug dose profile depicted in the upper plot is administered. The data of this dose was collected during a general anesthesia. The blue line represents the NMB level when the model is simulated under the conditions of scenario (1) and the red line is the NMB level for scenario (2). For a global analysis, scenarios (1) and (2) were applied to the hundred

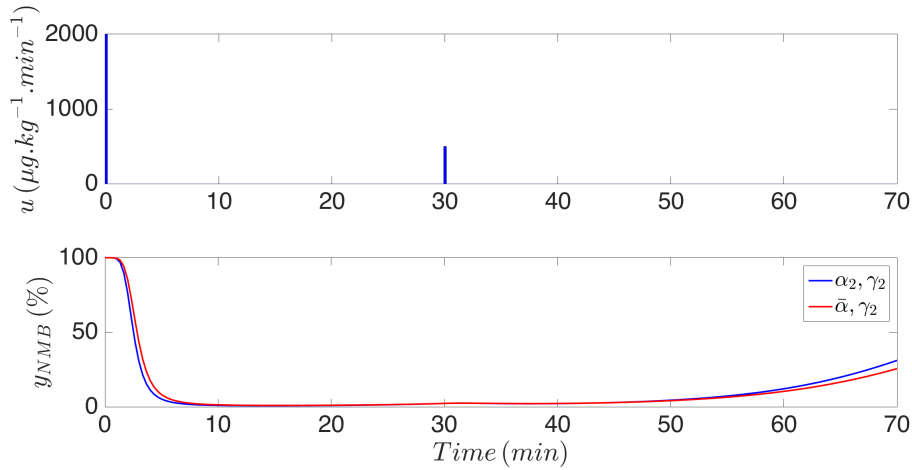


Figure 4.6: NMB level evolution for the scenarios (1) and (2) for patient number 2 for the real dose administered during surgery, consisting of an initial *bolus* followed by a second *bolus* at time instant $t = 30$ min.

models presented in Appendix B with the real drug dose signal of Figure 4.6. The average of each of response sets of signals was computed and illustrated in Figure 4.7. The maximum value of the relative difference between the NMB levels obtained under the conditions of scenario (1) and (2) is 5.92%.

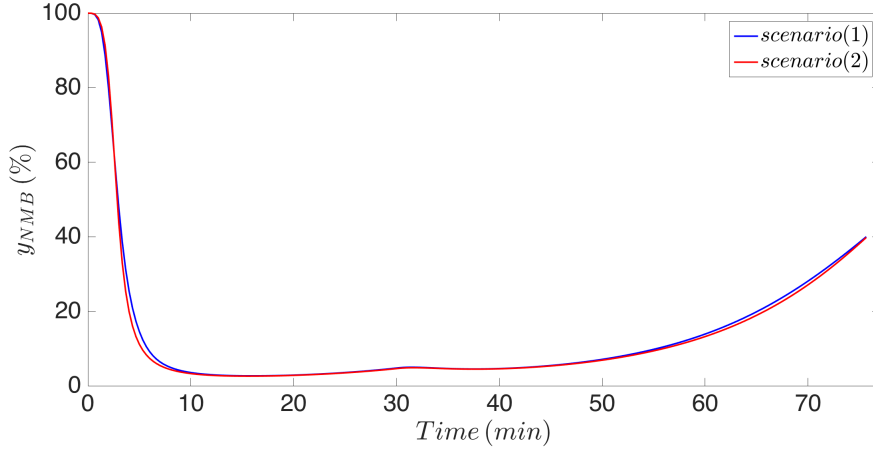


Figure 4.7: Mean value of NMB level evolution for the scenarios (1) and (2) for the hundred simulated models.

These results support the use of this approach to design a positive control law.

Figure 4.8 shows the performance of the controller using the simplified control (SC) for the same model of Figure 4.1, *i.e.*, using the data set of the patient number 17 of Appendix B ($\alpha_{17} = 0.0366$, $\gamma_{17} = 1.9262$) and using $\lambda = 0.2$. By comparing the two control schemes it is possible to see that the performance of the simplified control is similar with the performance of the controller when the parameters used to design the controller coincide with the parameters of the model. The significant difference is the velocity of convergence of the $M(x)$ to desired value M^* , and as was already said, this can be overcome by adjusting the design parameter λ , as it is possible to see in Figure 4.9 that shows the difference between the previous simulation when the parameter λ is adjusted. For λ equal to 0.5 the obtained results are closer to the results obtained with $\alpha = \alpha_i$ and $\gamma = \gamma_i$ ($i \in \{1, \dots, 100\}$).

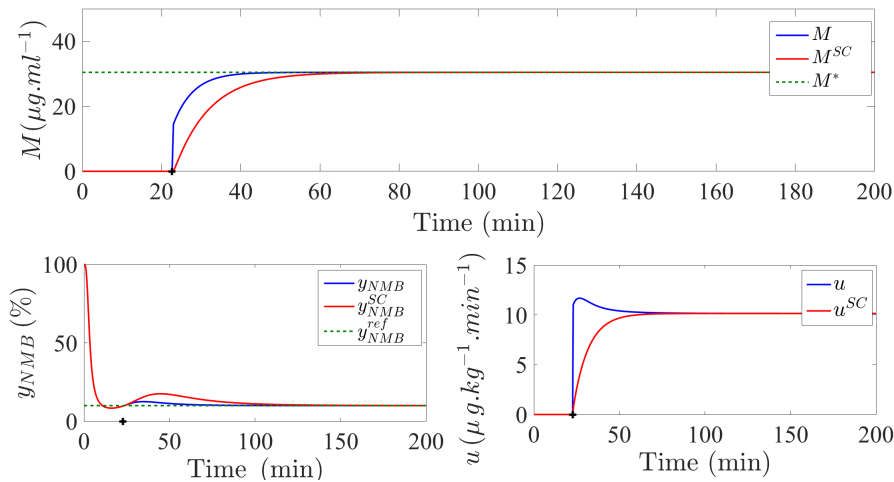


Figure 4.8: Comparison between the NMB level for the patient 17 obtained when the drug is determined by the positive control law (blue line) and the NMB level obtained when the drug is determined by the simplified positive control law (red line).

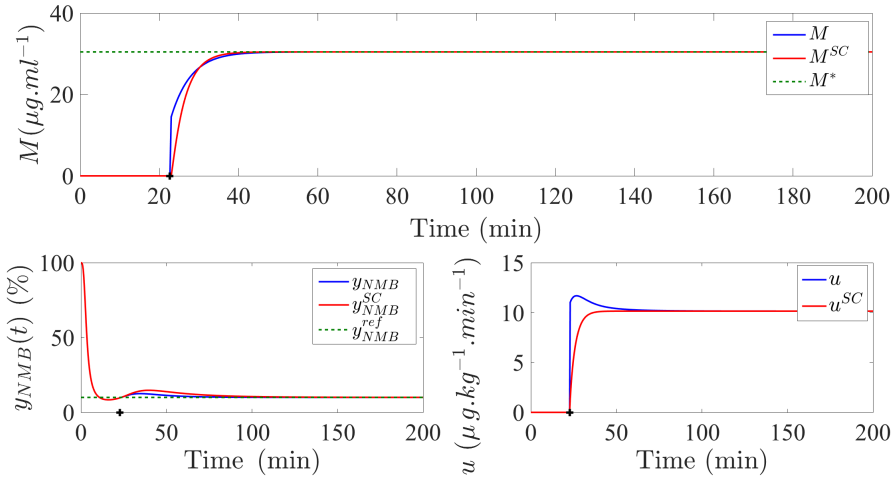


Figure 4.9: Comparison between the NMB level obtained when the drug is determined by the positive control law (blue line) with $\lambda = 0.2$ and the NMB level obtained when the drug is determined by the simplified positive control law (red line) with $\lambda = 0.5$.

4.2.2 Simplified control for *remifentanyl* and *propofol* - BIS case

Using the same reasoning as for the NMB case, simplified control laws for *propofol* and for *remifentanyl* can be defined as in equations (4.33) and (4.34), respectively,

$$\begin{cases} u^P(t) = \max(0, \tilde{u}^P(t)) \\ \tilde{u}^P(t) = -\frac{1}{d_3} ((d_2 - d_3)x_1^P + (d_1 - d_2)x_2^P - d_1x_3^P) - \frac{1}{d_3\bar{\xi}}\lambda (M(x^P(t)) - M^{*P}), \end{cases} \quad (4.33)$$

$$\begin{cases} u^R(t) = \max(0, \tilde{u}^R(t)) \\ \tilde{u}^R(t) = -\frac{1}{l_3} ((l_2 - l_3)x_1^R + (l_1 - l_2)x_2^R - l_1x_3^R) - \frac{1}{l_3\bar{\eta}}\lambda (M(x^R(t)) - M^{*R}), \end{cases} \quad (4.34)$$

where $\bar{\xi}$ and $\bar{\eta}$ are the mean values for the parameters ξ and η , respectively, and the desired values of, M^{*P} and M^{*R} , are obtained as,

$$\begin{aligned} M^{*P} &= \frac{3\rho z^{ref}}{\frac{1}{C_{50}^P}m\rho + \frac{1}{C_{50}^R}} \\ M^{*R} &= \frac{3z^{ref}}{\frac{1}{C_{50}^P}m\rho + \frac{1}{C_{50}^R}}, \end{aligned} \quad (4.35)$$

where z^{ref} is computed as,

$$z^{ref} = \left(\frac{97.7}{y_{BIS}^{ref}} - 1 \right)^{1/\zeta}. \quad (4.36)$$

Similarly to what was done for the NMB level, the following two scenarios were applied to validate this approach for the BIS case. The drug profile doses used to simulate the patient's response are the ones depicted in the lower plot of Figure 4.10 and correspond to the actual administered dose

during surgery.

The following two scenarios were considered:

1. The model is simulated with $\xi = \xi_i$, $\eta = \eta_i$, $m = m_i$ and $\zeta = \zeta_i$ ($i \in \{1, \dots, 18\}$);
2. The model is simulated with $\xi = \bar{\xi} = 0.0759$, $\eta = \bar{\eta} = 0.5825$, $m = m_i$ and $\zeta = \zeta_i$ ($i \in \{1, \dots, 18\}$);

The bottom plot of Figure 4.10 shows the comparison of the BIS level simulated for the model number 8 ($\xi_8 = 0.0860$, $\eta_8 = 0.0212$, $m_8 = 1.4203$ and $\zeta_8 = 0.9780$). The blue line represents the BIS level when the model is simulated under the conditions of the scenario (1) and the red line is the BIS level for scenario (2) and it is possible to see that the obtained BIS level is almost equal.

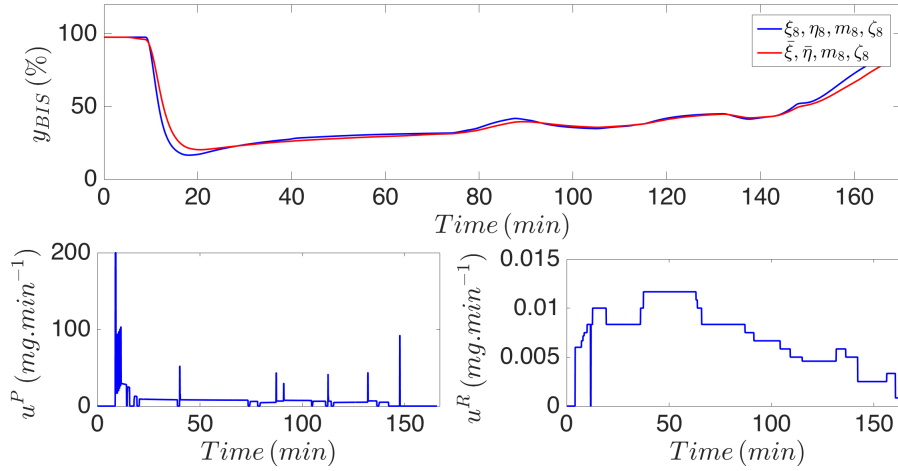


Figure 4.10: BIS level evolution for the scenarios (1) and (2).

In the same line of what was done for the NMB level, scenarios (1) and (2) were applied to the eighteen models presented in Appendix E with the drug dose signals of Figure 4.10. The mean of the signals were computed and illustrated in Figure 4.11. The maximum value between the relative difference between the BIS level obtained under the conditions of scenario (1) and (2) is 8.71%.

The results above the use of this approach to design suitable positive control laws.

Figure 4.12 shows the performance of the controller using the simplified control (SC) for the same model of Figure 4.4, *i.e.*, under the same conditions of patient number 18 and $\lambda = 5$. As it already happened for the NMB case, the two controller responses are similar. Again, the significant difference is the velocity of convergence of the BIS level to the BIS reference level. Figure 4.13 shows the difference of the controlled signal when the controller is designed with $\lambda = 10$. Although the convergence is not faster than the NMB case, these results give reason to its application in a clinical environment.

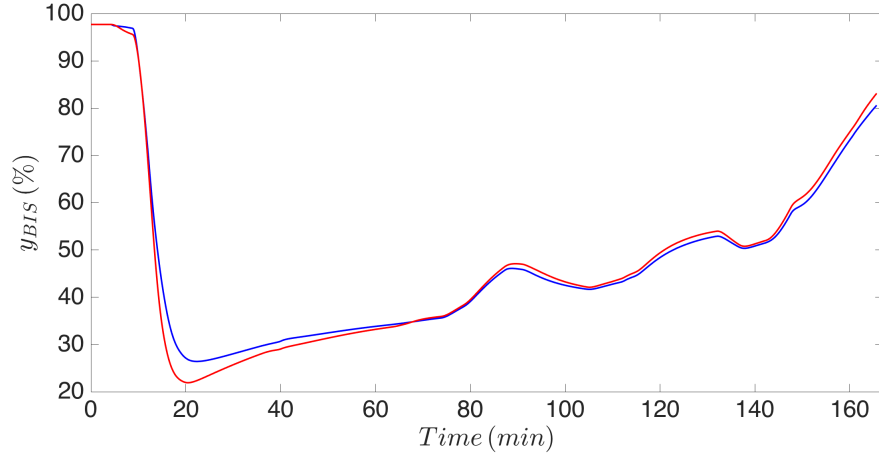


Figure 4.11: Average BIS level response evolution under scenarios (1) and (2) for the eighteen simulated models.

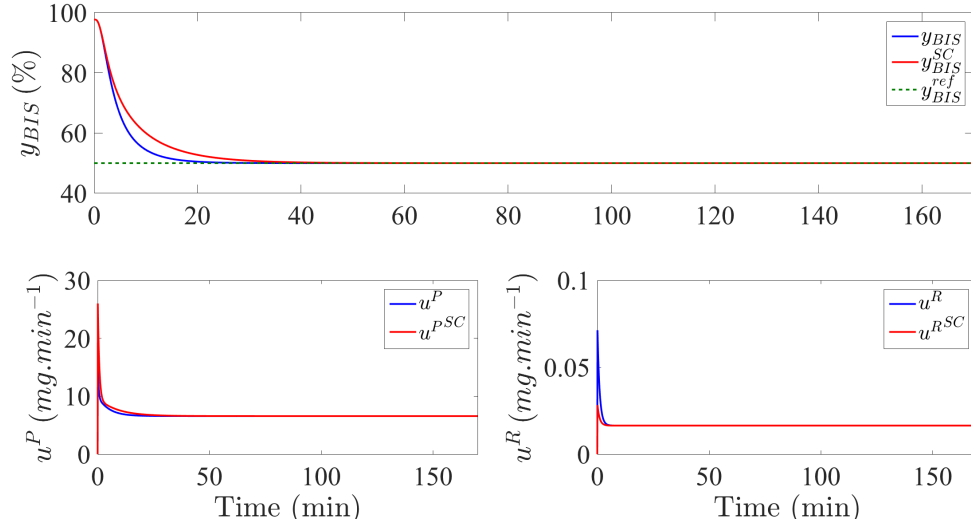


Figure 4.12: Comparison between the BIS level obtained when the drug doses are determined by the positive control laws (blue line) and the BIS level obtained when the drug doses are determined by the simplified positive control laws (red line).

4.3 Control scheme with parameter identification

In the previous simulations we assume that the patient dependent parameters are known and consequently the exact control law is also known. However, this does not happen in a real environment. So, with the purpose to apply the proposed simplified positive control law in the real environment, a control scheme with parameter identification is proposed in this section.

Figure 4.14 schematizes the control scheme for drug administration with identification. The signals $u(t)$ and $y(t)$ are the input signals for the extended kalman filter (EKF). Until a certain time instant, this algorithm learns with the real signals and identifies the patient dependent parameters. The parameters identified are used to simulate the patient and to design the controller law that

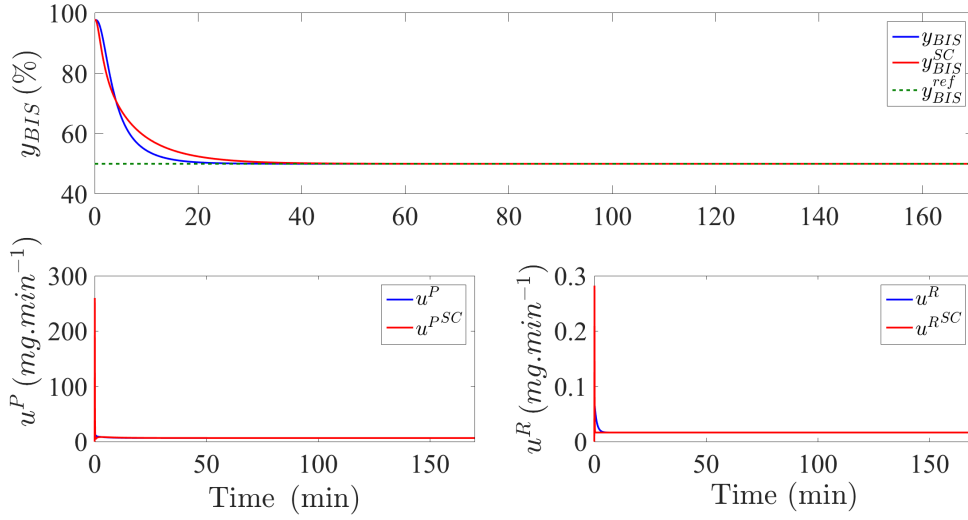


Figure 4.13: Comparison between the BIS level obtained when the drug doses are determined by the positive control laws (blue line) with $\lambda = 5$ and the BIS level obtained when the drug doses are determined by the simplified positive control laws (red line) with $\lambda = 10$.

computed the system input, $u(t)$. In the next two sections the results for the NMB control and for

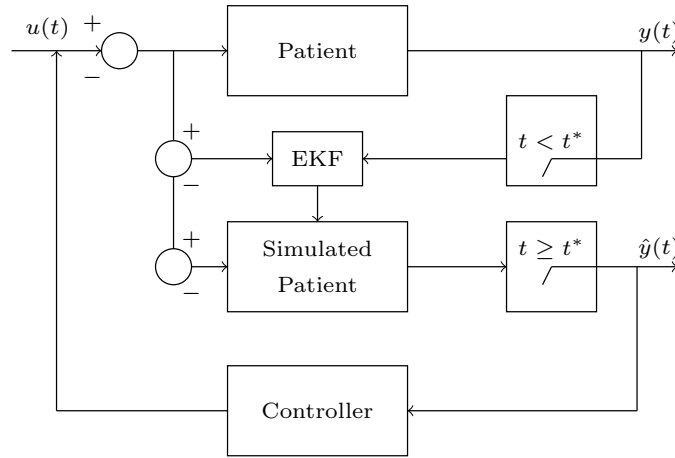


Figure 4.14: Block diagram of the control scheme where the patient dependent parameters are identified by the EKF algorithm.

the BIS control when this control scheme is applied are presented.

4.3.1 Simplified control scheme for atracurium - NMB case

Applying the scheme of Figure 4.14 to the NMB case, the control approach is summarized by the following steps:

1. An initial *bolus* of *atracurium* is administered to the patient;

2. After a certain time instant, the patient begins to recover from the initial *bolus*. This time instant is obtained using the algorithm OLARD, Silva et al. (2009). This algorithm detects the initial recovery time, t^* . At this time instant, the continuous drug infusion starts;
3. For $t < t^*$, the algorithm EKF identifies the patient dependent parameter γ .
4. For $t \geq t^*$, the control law (4.31) computes the *atracurium* dose using $\alpha = \bar{\alpha}$ and $\gamma = \hat{\gamma}(t^*)$;
The drug dose is computed in order to achieve the desired value of 10% for the NMB level.

To validate this approach the data of 10 real cases collected during a general anesthesia were used. More concretely, a comparison between the amount of drug given by the anesthesiologist and the controller was performed. The profile of these real responses and the real doses are illustrated in Appendix C. The data set is composed by six female cases with 58 ± 19 years of age and four male cases with 60 ± 22 years of age.

In Figure 4.15, it is possible to see the comparison between the amount of drug given by the anesthesiologist and the amount of the drug computed by the control scheme presented in this thesis. The bottom plot shows the NMB level obtained by administering the controlled drug dose. The data of this simulation corresponds to the data of patient number 8 of Appendix C. The case depicted in Figure 4.15 is a good case to show that the use of a controller allows to stabilize the patient's response. The controller begins at $t^* = 31 \text{ min}$ (time instant determined by the algorithm OLARD) and was designed with $\bar{\alpha} = 0.0382$ and $\hat{\gamma} = 2.558$ (value obtained by the identification performed by the EKF at $t = t^*$).

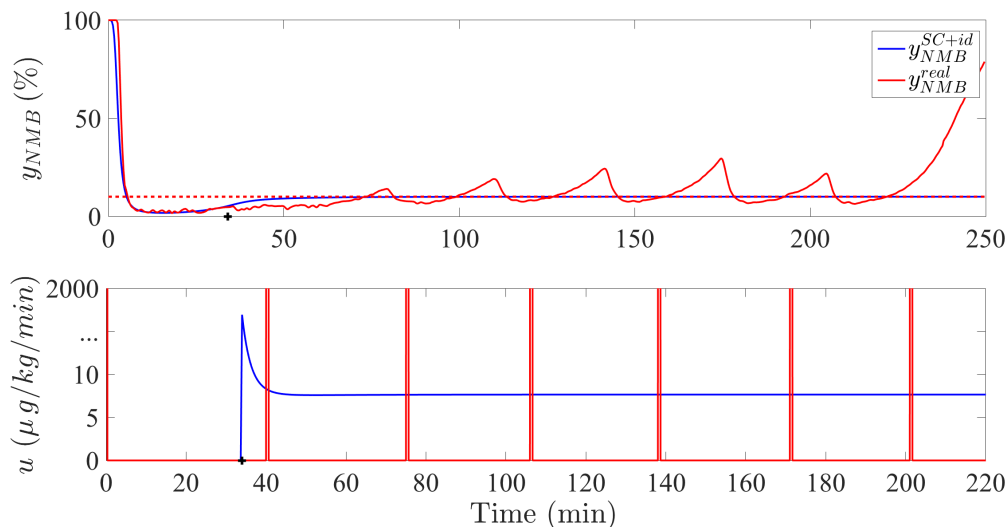


Figure 4.15: In the upper plot the *atracurium* dose given by the control scheme (red line) is represented and compared with the dose administered by the clinician in a general anesthesia (blue line). The bottom plot shows the corresponding NMB level. y_{NMB}^{SC+id} represents the NMB level obtained by applying the simplified control with parameter identification and y_{NMB}^{real} represents the real NMB level collected during the general anesthesia procedure.

In this example, the total amount of *atracurium* given by the controller is higher ($\sum u^{SC} = 7065 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) than the total real amount ($\sum u^{real} = 5000 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).

Figure 4.16 shows the difference between the total amount of *atracurium* dose administered during the general anesthesia and the total amount dose obtained by the controller for all the 10 cases. As it is possible to see, the total amount of dose is always higher in the case it is computed by the proposed control scheme. However, this is compensated by an NMB level closer to the reference NMB level 10%. This fact is illustrated in Figure 4.17, which represents the mean of the NMB level between in the time interval $[t_i, t_f]$, where t_i corresponds to the first time instant when the NMB level is lower than 10%. This time instant was chosen to analyze the NMB level without considering the abrupt variation in the beginning of the anesthesia procedure. The time instant t_f corresponds to the time where the surgery ends.

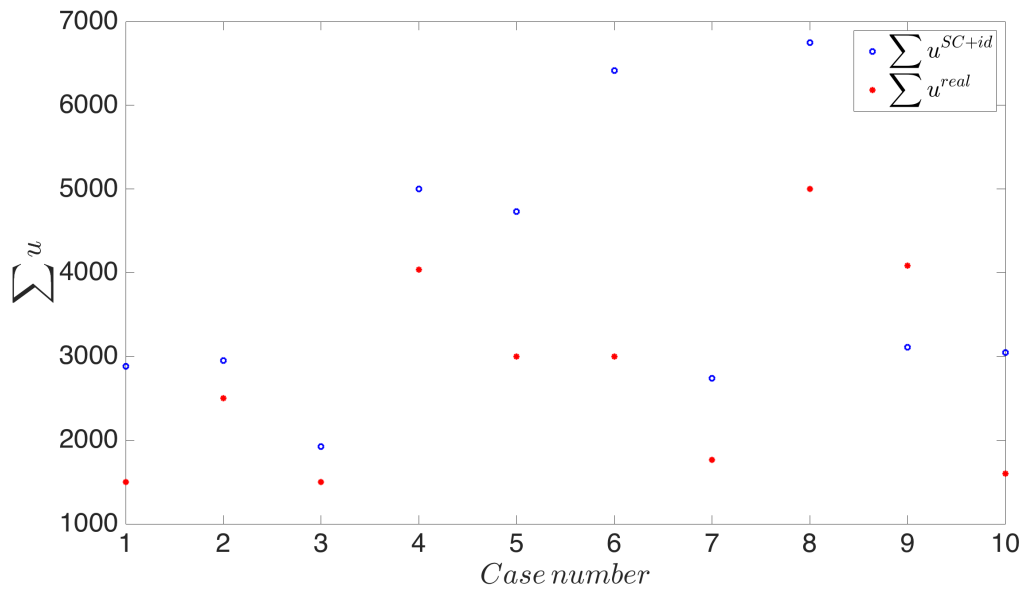


Figure 4.16: Total amount of *atracurium* administered during the surgery (red star) and the total amount determined by the control scheme (blue bullet). $\sum u^{SC+id}$ represents the total amount dose obtained by the simplified control with parameter identification and $\sum u^{real}$ represents total amount of the real dose administered during general surgeries.

In order to analyze the trade-off between the amount of the drug and the NMB level, for each case, the following cost functional was considered

$$J = \frac{1}{n} \sum_{t=0}^n \left(\left(y_{NMB}^{ref} - y_{NMB}(t) \right)^2 + \kappa u^2(t) \right), \quad (4.37)$$

where the gain κ was chosen to be equal to 1. This choice was made to be in accordance with the weight parameters chosen for the optimal control problem in the next chapter.

Figure 4.18 shows the difference of the cost for the 10 real cases and the cost for these cases when the control scheme was applied.

As it is possible to see the cost functional is higher when the real signals $y_{NMB}(t)$ and $u(t)$ are considered. In order to justify and to reflect the real behavior in the control scheme, the NMB reference level was changed for the mean value of the real NMB level presented in Figure 4.17

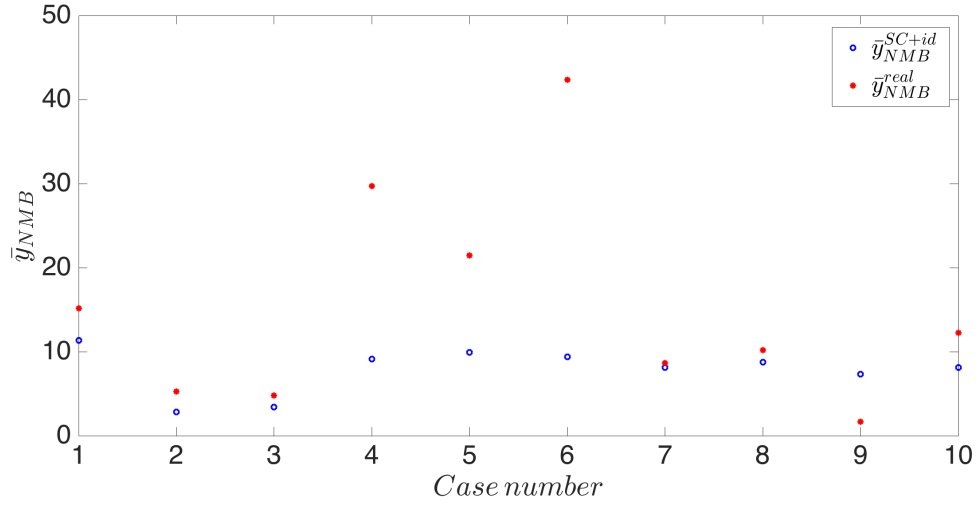


Figure 4.17: Mean of the real NMB level between the time instants t_i and t_f (red star) and mean of the simulated NMB level in the same time interval (blue bullet). t_i is the first time instant where the response is lower than 10% and t_f is the time instant when the surgery ends. $\bar{y}_{NMB}^{SC+id}$ represents the mean of the NMB level between in the time interval $[t_i, t_f]$ obtained by the simplified control with parameter identification and $\bar{y}_{NMB}^{real}$ represents the mean of the real NMB level between in the time interval $[t_i, t_f]$.

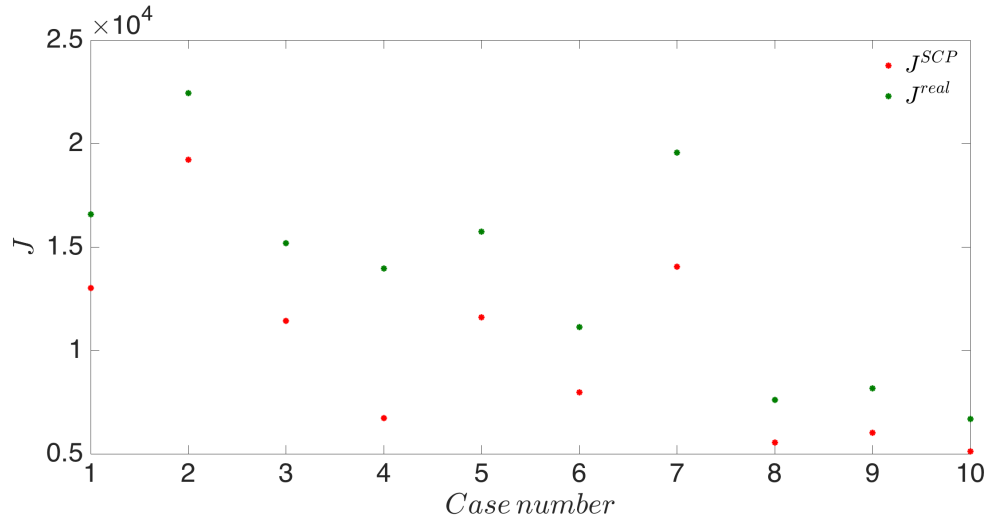


Figure 4.18: Cost value obtained for the real cases (blue bullet) and the cost value obtained for the control scheme (red star). J^{SC+id} represents the cost value obtained using the signals obtained by the simplified control with parameter identification and J^{real} represents the cost value obtained using the real signals obtained during general surgeries.

(red star). As expected, the total amount of drug given by the controller decreases, but is still higher than the total amount of the real drug administered. However, as it is possible to see in Figure 4.19, the difference is smaller than the difference depicted in Figure 4.16.

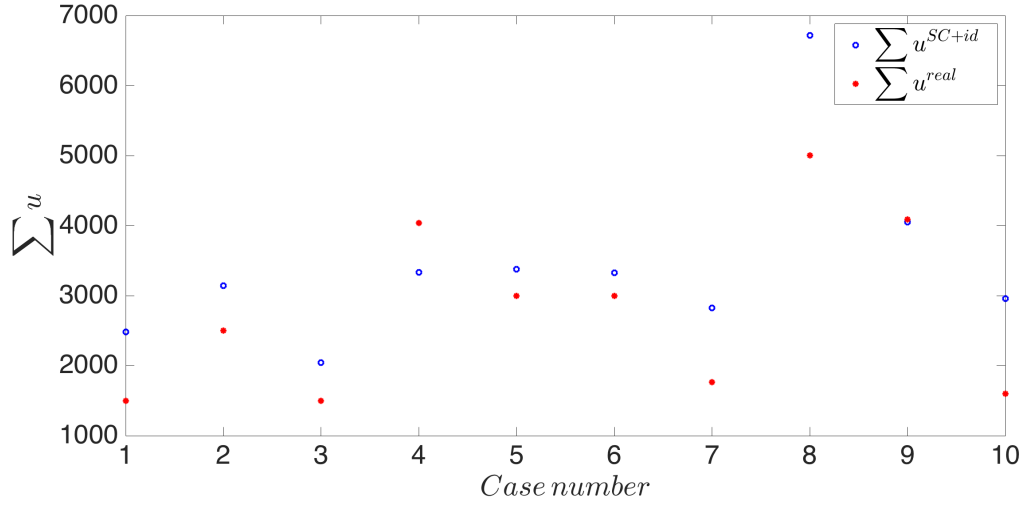


Figure 4.19: Total amount of *atracurium* administered during the surgery (red star) and the total amount determined by the control scheme (blue bullet) when the NMB reference level is taken to be equal to the mean of the real NMB level between the time instants t_i and t_f . t_i is the first time instant where the response is lower than 10% and t_f is the time instant when the surgery ends.

4.3.2 Simplified control scheme for *remifentanyl* and *propofol* - BIS case

This section presents the results for the proposed control scheme for the BIS case. The control approach is applied according the same scheme as in Figure 4.14. There are, however, some differences with respect to the NMB case, as an initial drug *bolus* is not given. The procedure is now as follows.

1. The anesthesiologists start the continuous infusion of *propofol* and *remifentanyl*;
2. For $t < t^* = 4 \text{ min}$ the EKF algorithm identifies the patient dependent parameters m and ζ . The instant t^* was empirically chosen based on the minimal time during which the two drugs are administered in the real cases;
3. For $t \geq t^* = 4 \text{ min}$ the control laws (4.33) and (4.34) compute the amount of *propofol* and *remifentanyl*, respectively, using $\xi = \bar{\xi}$, $\eta = \bar{\eta}$, $m = m(t^*)$ and $\zeta = \zeta(t^*)$. The dosages u^P and u^R of the two drugs are computed in order to achieve a BIS reference level of 50%. The chosen relation between these dosages is $u^P = \rho u^R$ with $\rho = 400$.

This approach was validated using the data presented in Appendix E. Figure 4.20 shows the performance of the control scheme for a patient with the same data as patient number 18. The EKF algorithm identified the parameters m and ζ at $t^* = 4 \text{ min}$ and the values obtained were $m(t^*) = 1.998$ and $\zeta(t^*) = 1.001$. Unlike for the NMB case, for the BIS the total amount of drug is higher in the real practice than using the control law. Moreover, the simulated BIS level obtained with the controller is closer to the BIS reference level 50% (desired level during a general anesthesia).

The performance of the control scheme was evaluated in the same way as for the NMB case. Figure 4.21 illustrates the amount of drugs actually administered during the real surgery and the

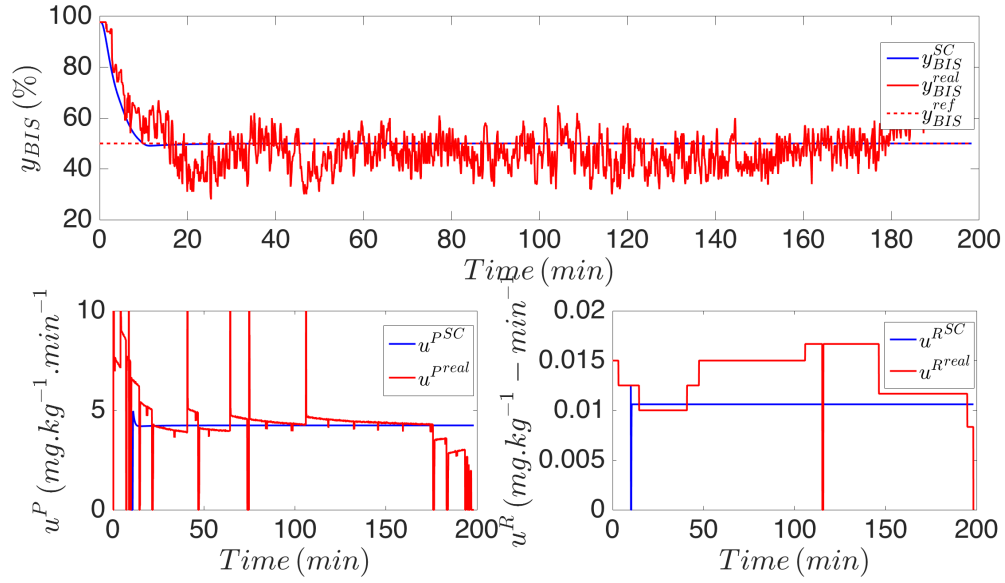


Figure 4.20: The upper plot shows the BIS level obtained when the profile of the drug doses represented in the bottom plot are administered. y_{BIS}^{SC} represents the BIS level obtained using the simplified controller, y_{BIS}^{real} is the real BIS level signal and y_{BIS}^{ref} is the BIS reference level; u^{PSC} and u^{Preal} represent the *propofol* doses obtained by the simplified controllers and the ones obtained for the real cases (in clinical environment), respectively, and u^{RSC} and u^{Real} represent the *remifentanyl* doses obtained by the simplified controllers and the ones obtained for the real cases (in clinical environment), respectively.

ones computed by the controllers, whereas Figure 4.22 shows the mean value of the corresponding BIS levels between t_i and t_f . Figure 4.23 shows the cost functional (4.38) obtained with the real signals and the one obtained with the simulated signals. In this case, the time instant t_i corresponds to the first time instant when the real response is lower than the desired value 50% and t_f represents the end of the surgery.

The cost functional for the BIS level was computed using the following equation,

$$J = \frac{1}{n} \sum_{t=0}^n \left(\left(y_{BIS}^{ref} - y_{BIS}(t) \right)^2 + \kappa \left(u^P(t) + u^R(t) \right)^2 \right), \quad (4.38)$$

$\kappa = 10$, according the value chosen in the next chapter.

As it is possible to see, the cost functional is higher for the real cases, which means that the trade-off between the amount of drug administered and the tracking of the BIS reference is worst than the control approach. These results encourage the application of this control scheme in real environment.

An advantage of using an online identification method is the possibility of readjusting the parameter estimation and consequently to adjust the control scheme. Figure 4.24 shows the difference between the BIS evolution for the patient number 13 when the parameters are identified only at $t^* = 4 \text{ min}$ and when the parameters are identified in two different instant times, $t^* = 4 \text{ min}$ and $t^* = 8 \text{ min}$. In the latter case, the variability of the parameter identification was low, the parameter

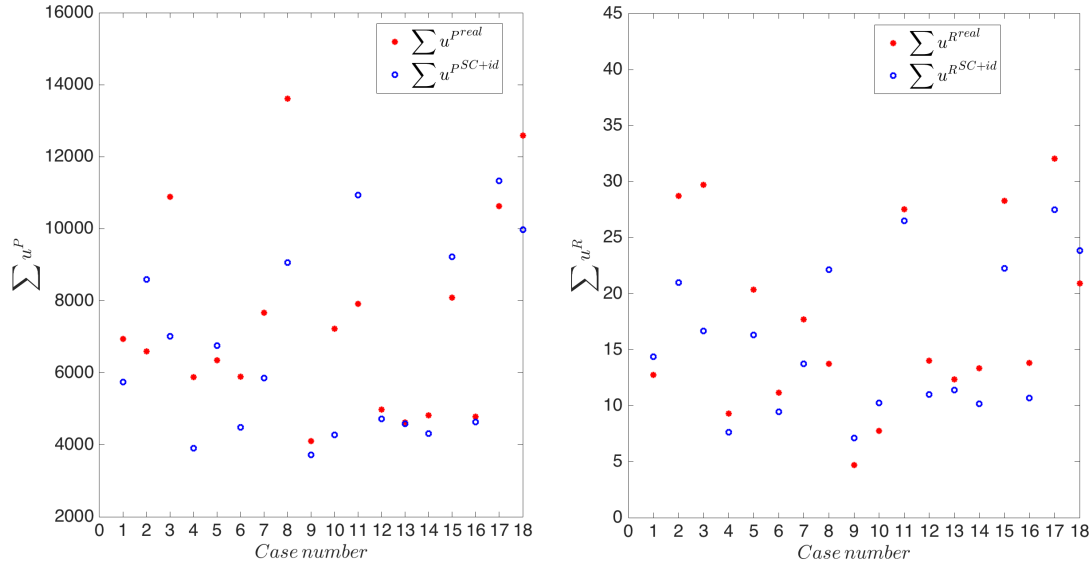


Figure 4.21: The left plot represents the total amount of *propofol* administered during the surgery (red star) and the total amount determined by the control scheme (blue bullet). The right plot presents the total amount of administered *remifentanyl* in the same conditions. $\sum u^{P^{SC+id}}$ and $\sum u^{P^{real}}$ represent the *propofol* doses obtained by the simplified controllers with parameter identification and the ones obtained for the real cases (in clinical environment), respectively, and $\sum u^{R^{SC+id}}$ and $\sum u^{R^{real}}$ represent the *remifentanyl* doses obtained by the simplified controllers with parameter identification and the ones obtained for the real cases (in clinical environment), respectively.

m remained the same and the parameter ζ changed from 2 to 1.999. However, as it is possible to see in Figure 4.24 the obtained response is considerably better.

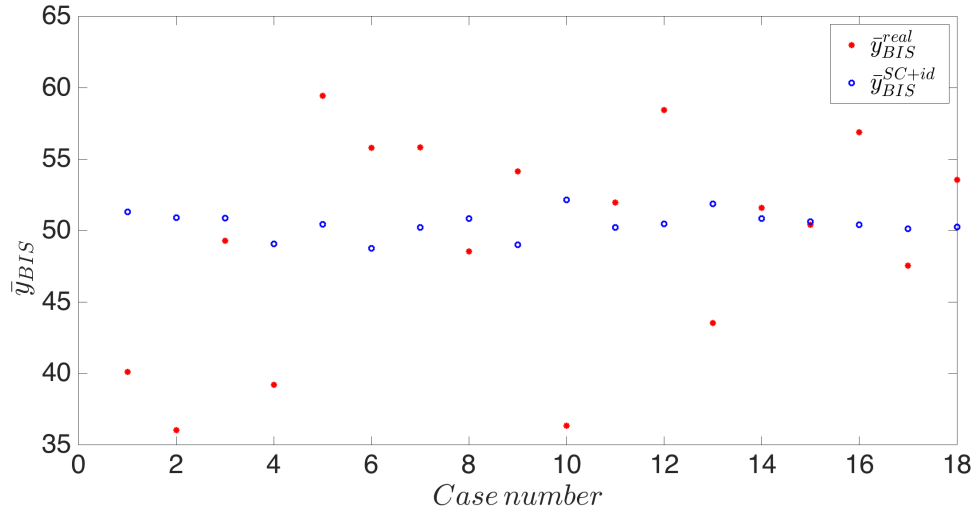


Figure 4.22: Mean of the real BIS level between the time instants t_i and t_f (red star) and mean of the simulated NMB level in the same time interval (blue bullet). t_i is the first time instant where the response is lower than 50% and t_f is the time instant when the surgery ends. $\bar{y}_{BIS}^{SC+id}$ represents the mean of the BIS level between in the time interval $[t_i, t_f]$ obtained by the simplified control with parameter identification and $\bar{y}_{BIS}^{real}$ represents the mean of the real BIS level between in the same time interval.

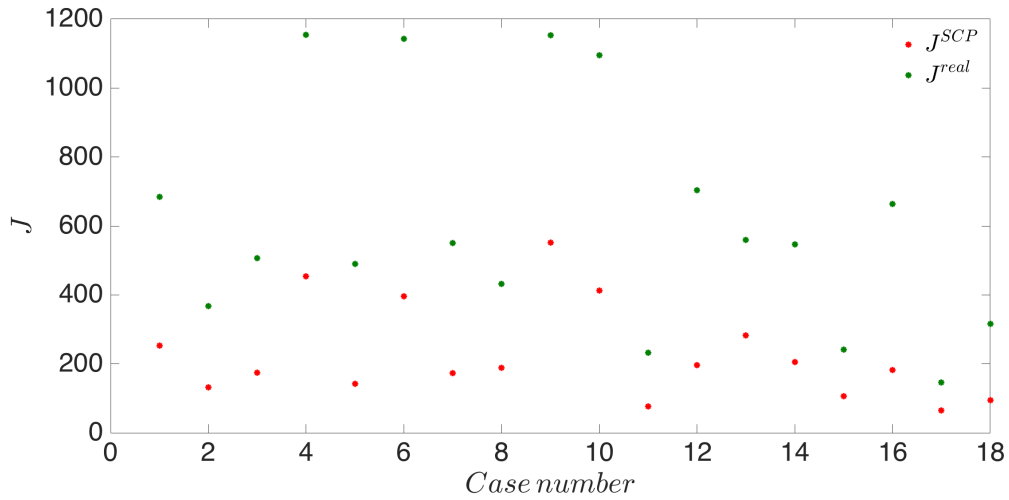
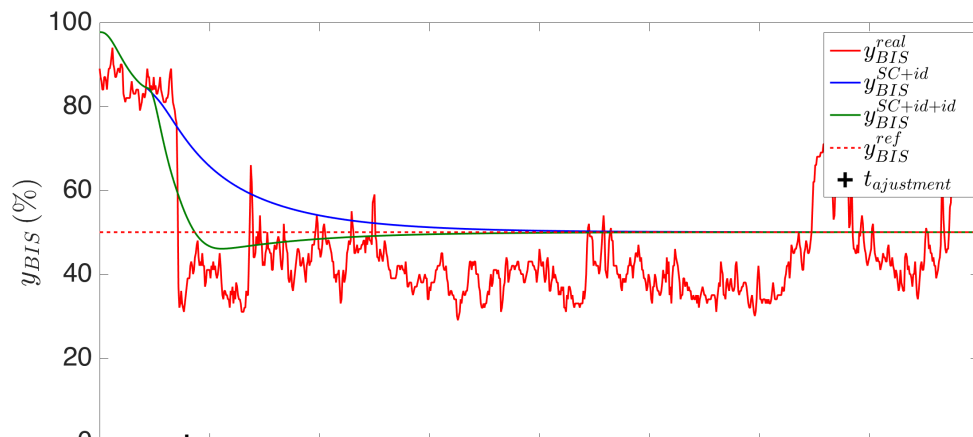


Figure 4.23: Cost values obtained for the real cases (blue bullet) and for the control scheme (red star). J^{SC+id} represents the cost value obtained using the signals obtained by the simplified control with parameter identification and J^{real} represents the cost value obtained using the real signals obtained during the general surgery.



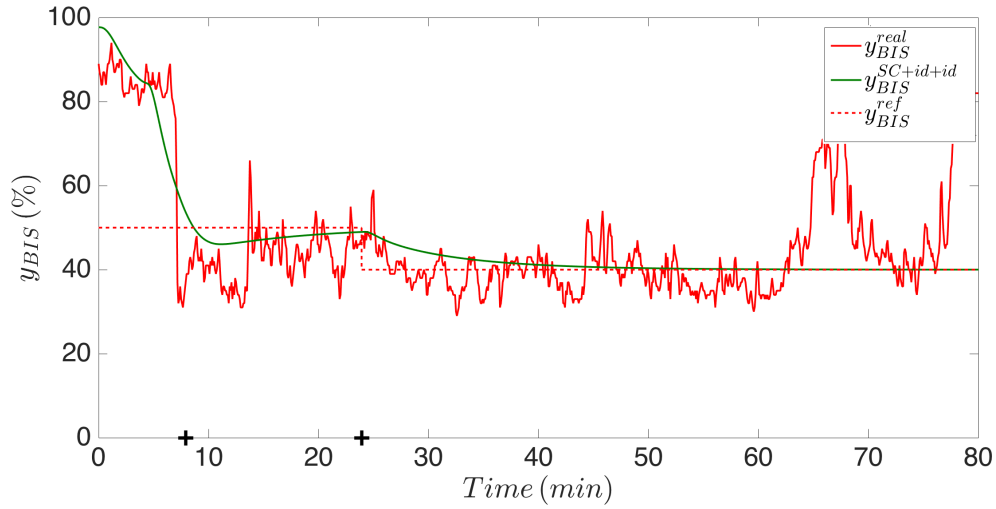


Figure 4.25: Comparison between the BIS response when the parameters are identified at $t^* = 4\text{min}$ and $t^* = 8\text{min}$. The two markers in the x-axis, respectively, indicate the instants when the parameters and the BIS reference level were readjusted. y_{BIS}^{real} represents the real BIS level collected during the general anesthesia procedure, $y_{BIS}^{SC+id+id}$ represents the BIS level obtained by readjusting of the simplified control and y_{BIS}^{ref} represents the BIS reference level.

Moreover, as it is possible to see in Figure 4.25, the law patient's response adapts well its behavior when there is a change in the desired BIS reference level used in the control law, during the procedure. Figure 4.25 shows the performance of the control scheme when the parameters identification are readjusted at $t^* = 8\text{min}$ and when the BIS reference level is chosen to be equal to 40% after $t = 23\text{min}$. The change of the BIS reference level may be necessary due to clinical demands.

In this chapter, a simplified positive control law was proposed, and its simulated application in the real environment was compared, through a cost functional, with the real patient responses to the drug administered by the anesthetist.

5

Controllers based on optimal control

This section presents a state-feedback controller design method based on optimal control. Here the reference tracking problem is formulated as an optimal control problem with inequality constraints in the input. In turn, the optimal control problem (OCP) is relaxed into a semi-definite program (SDP) by replacing the original variables by their moments up to a certain order in the same line of what is done in Lasserre (2009), Lasserre et al. (2008). The optimal values of the moments can then be computed by semi-definite programming solvers Sturm (2013), Lofberg (2004), Grant and Boyd (2015) and the gains of the state-feedback control law are then computed based on these values. Although the obtained control law is only an approximation of the optimal solution, this approach has the advantage of easily coping with state and input constraints.

We formulated the output optimal control problem for the reference tracking problem in terms of optimal control as follows. Suppose that, given a state-space system

$$\begin{cases} \dot{x} &= Ax + Bu \\ c &= Cx \end{cases} \quad (5.1)$$

one wishes to design a positive control law so as to obtain $u(t) \geq 0$ that drives the system output c to a reference value c_e . Assume further that the output reference value c_e corresponds to a system set-point (equilibrium) $(x(t), u(t), c(t)) \equiv (x^e, u^e, c^e)$, for $t \geq 0$. Such set-point can be computed from the equations:

$$\begin{cases} 0 &= Ax^e + Bu^e \\ c^e &= Cx^e \end{cases} \quad (5.2)$$

Define the following errors with respect to the set-point: $\hat{x}(t) = x(t) - x^e$, $\hat{u}(t) = u(t) - u^e$ and $\hat{c}(t) = c(t) - c^e$. Clearly, the new variables satisfy the equations:

$$\begin{cases} \hat{x}(t) &= A\hat{x} + B\hat{u} \\ \hat{c}(t) &= C\hat{x} \end{cases} \quad (5.3)$$

Finally, consider the optimal control problem:

$$\begin{aligned} \min_{\hat{u}(t), t_f} J(\hat{x}(t), \hat{u}(t)) &= \frac{1}{2} \int_{t^*}^{t_f} \underbrace{\hat{x}^T(t) Q \hat{x}(t) + \hat{u}^T(t) R \hat{u}(t)}_{h(\hat{x}(t), \hat{u}(t))} dt \\ \text{s.t. } \hat{\dot{x}}(t) &= \underbrace{A\hat{x}(t) + B\hat{u}(t)}_{f(\hat{x}(t), \hat{u}(t))} \\ \hat{x}(t^*) &= \hat{x}_0 \\ \hat{x}(t_f) &= [0 \ \dots \ 0]^T \\ \hat{u}(t) &\in \mathcal{G} \end{aligned} \quad (5.4)$$

where $Q = Q^T > 0$ and $R = R^T > 0$ are design matrices, t^* is the time instant when the controller action begins, $h(\hat{x}(t), \hat{u}(t))$ and $f(\hat{x}(t), \hat{u}(t))$ are homogeneous quadratic polynomial functions and $\mathcal{G}$ is the constrained region for the input values, $\hat{u}$, which is a set defined as

$$\mathcal{G} = \{\hat{u}(t) : g(\hat{u}(t)) \geq 0, \forall t \geq 0\},$$

where $g(\hat{u}(t))$ is a polynomial function.

Note that the final state restriction $\hat{x}(t_f) = [0 \ \dots \ 0]^T$ forces the tracking error to be zero at time t_f .

LMI relaxation into a semi-definite program

This section follows closely the method proposed in Lasserre (2009), Lasserre et al. (2008). In order to obtain an approximate solution of the previous OCP, a change of variables to transform this problem into an SDP is made. For this purpose the new variables are defined as the moments of $\bar{x} = (\hat{x}, \hat{u})$, *i.e.*,

$$y_\beta = \int_0^T \bar{x}^\beta dt, \quad (5.5)$$

where $\beta = (\beta_1, \dots, \beta_n, \beta_{n+1})$ is a multi-index, $\bar{x}^\beta = \prod \bar{x}_i^{\beta_i}$ and T is the final time instant.

To transform a polynomial into a moment we follow a similar procedure to what is done in Lasserre (2009). To that end, given a polynomial $p(\bar{x}) = \sum_{\beta \in \mathbb{N}^{n+1}} p_\beta \bar{x}^\beta$, a linear bounded functional

L is defined as

$$L(p) = \sum_{\beta \in \mathbb{N}^{n+1}} p_{\beta} y_{\beta} . \quad (5.6)$$

This amounts to replacing the monomials in p by the corresponding integrals, according to (5.5). Based on the moments y_{β} with $\beta \in \mathcal{B}_d \stackrel{\text{def}}{=} \{(\beta_1, \dots, \beta_{n+1}) \in \mathbb{N}^{n+1} : \sum_{j=1}^{n+1} \beta_j \leq d\}$ one also introduces the moment matrix of order d , $M_d(y)$, which plays an important role in the reformulation of the OCP (5.4). The moment matrix has rows and columns labeled by

$$V_d(\bar{x}) = \left[1, \bar{x}_1, \dots, \bar{x}_{n+1}, \bar{x}_1^2, \bar{x}_1 \bar{x}_2, \dots, \bar{x}_1 \bar{x}_{n+1}, \bar{x}_2^2, \bar{x}_2 \bar{x}_3, \dots, \bar{x}_2 \bar{x}_{n+1}, \dots, \bar{x}_{n+1}^2, \dots, \bar{x}_{n+1}^d \right] \quad (5.7)$$

and is constructed as

$$M_d(y) = L(V_d(\bar{x}) V_d(\bar{x})^T) \quad (5.8)$$

with L as defined in (5.6). This means that L is applied to each entry of the matrix $V_d(\bar{x}) V_d(\bar{x})^T$. As a consequence, the cost functional $J(\hat{x}(t), \hat{u}(t))$ can be rewritten as

$$L(h) = \frac{1}{2} \sum_{\beta} h_{\beta} y_{\beta} , \quad (5.9)$$

where h_{β} are the coefficients of the polynomial $h(\hat{x}(t), \hat{u}(t))$ in the OCP formulation (5.4).

To incorporate the system dynamics and the end-point constraints as constraints of the semi-definite program, monomial test functions $v(\hat{x})$ are considered. These functions are polynomials given by $v(\hat{x}) = \hat{x}^{\beta}$. Note that, on one hand, from the Fundamental Theorem of Calculus:

$$\int_0^T \frac{dv(\hat{x}(t))}{dt} dt = v(\hat{x}(T)) - v(\hat{x}(0)) , \quad (5.10)$$

and on the other hand, using the chain rule and the system dynamics the total time derivative is equal to:

$$\frac{dv(\hat{x})}{dt} = \frac{\partial v}{\partial \hat{x}} \cdot \frac{d\hat{x}}{dt} = \frac{\partial v}{\partial \hat{x}} \cdot f(\hat{x}(t), u(t)) . \quad (5.11)$$

Thus for each function $v(\hat{x})$ one obtains:

$$\int_0^T \frac{\partial v}{\partial \hat{x}} \cdot f(\hat{x}(t), \hat{u}(t)) dt = v(\hat{x}_T) - v(\hat{x}_0) \quad \forall v . \quad (5.12)$$

Since f is a polynomial function of $\hat{x}$ and $\hat{u}$ and v and $\frac{\partial v}{\partial \hat{x}}$ are polynomial functions of $\hat{x}$ this equation can be rewritten in terms of the moments as $\sum_j a_{ij} y_{\alpha_j} = b_i$, where a_{ij} are the coefficients of the moments for $i = 1, \dots, M$. The positive integer M represents the number of all possible combinations of the exponents in the polynomial $v(\hat{x})$ so that they are not all zero and their sum is less or equal to d . For better understanding, consider the following example: if there are three state

variables then $v(\hat{x}) = \hat{x}_1^{\beta_1} \hat{x}_2^{\beta_2} \hat{x}_3^{\beta_3}$ and if $d = 2$ then all possible combinations such that $\beta_1 + \beta_2 + \beta_3 \leq d$ yield $M = 9$ as will be detailed in subsection 5.1.

To handle the state and input constraints the localizing matrix $M_d(gy)$ with respect to y and to the polynomial $g(\hat{u}(t))$ is defined. This matrix is given by

$$M_d(gy) = L(gV_d(\bar{x})V_d(\bar{x})^T), \quad (5.13)$$

with $V_d(\bar{x})$ defined in (5.7). The dimensions of $M_d(gy)$ will be such that its entries are moments of order less or equal to d . Therefore, $M_d(gy)$ is always of smaller dimension than $M_d(y)$. The OCP (5.4) can then be rewritten as

$$\begin{aligned} \min_y \quad & L(h) \\ \text{s.t.} \quad & \sum_j a_{ij} y_{\alpha_j} = b_i, \quad i = 1, \dots, M \\ & M_d(y) \geq 0 \\ & M_d(gy) \geq 0 \end{aligned} \quad (5.14)$$

According to Lasserre (2009), the advantage of reformulating the original problem as a SDP is that this approximation has revealed to be fast from a computational point of view and often presents finite convergence to the global optimum.

This problem is solved using software with an SDP solver such as the ones proposed in Sturm (2013), Lofberg (2004), Grant and Boyd (2015), and the values of the optimal moments $y_\beta = y_\beta^*$ are obtained. Then, a state feedback control input

$$\hat{u}(t) = \sum_{i=1}^n K_i \hat{x}_i(t) . \quad (5.15)$$

with unknown gains K_i can be determined by replacing (5.15) in the moments that involve $\hat{u}$ and recasting them in terms of the moments involving the state. For instance, for a simple system with two state components, $\hat{x}_1, \hat{x}_2$ and one input $\hat{u}$, the moment y_{101} , where the first index indicates the order of the moment in $\hat{x}_1$, the second index in $\hat{x}_2$ and the third index in $\hat{u}$, becomes:

$$\begin{aligned} y_{101} &= \int_0^T \hat{x}_1(t) \hat{u}(t) dt = \int_0^T \hat{x}_1(t) (K_1 \hat{x}_1(t) + K_2 \hat{x}_2(t)) dt \\ &= \int_0^T K_1 \hat{x}_1^2(t) + K_2 \hat{x}_1(t) \hat{x}_2(t) dt \\ &= K_1 y_{200} + K_2 y_{110} \end{aligned} \quad (5.16)$$

Proceeding in the same way for the other moments involving the input yields a system of linear equations where the unknowns are the feedback gains and the coefficients and independent terms

are the moments. After the values of the optimal moments are obtained the feedback gains can be computed whenever the system of linear equations has a solution.

Remark: Note that two approximations have been made that led to the LMI relaxation when compared to the original problem. First, the considered moment matrix has finite order d . Although, the approximation converges to the optimal solution $d \rightarrow \infty$ (under some mild assumptions stated in Lasserre (2009), Lasserre et al. (2008)), the theoretical guarantees on the input verifying the constraints in the case of the original optimal control problem might be lost in the relaxed solution for a finite d . For linear quadratic problems the hope is that an order $d = 2$ will be enough based on what happens for the Linear Quadratic Gaussian (LQG) problem, Bellman (1957), but there is no guarantee that this is correct when there are constraints on the state and/or on the input. Due to this reason, it is necessary to check a-posteriori in simulation if the obtained approximate solution indeed satisfies the original constraints for the set of possible initial conditions of interest to a given application. Second, after computing the approximation of order d for the moment matrix we assumed that the control input was a linear state feedback. Therefore, the solution to this problem (*i.e.*, the computed optimal moments and corresponding feedback gain) is only an approximation to the solution of the OCP.

5.1 Optimal control for *atracurium* - NMB case

To design a feedback control law to track a desired NMB reference level, y_{NMB}^{ref} , the optimal control problem is formulated as:

$$\begin{aligned} \min_{\hat{u}(t), t_f} J(\hat{x}(t), \hat{u}(t)) &= \frac{1}{2} \int_{t^*}^{t_f} \hat{x}^T(t) Q \hat{x}(t) + \hat{u}^T(t) R \hat{u}(t) dt \\ \text{s.t. } \hat{\dot{x}}(t) &= A \hat{x}(t) + B \hat{u}(t) \\ \hat{x}(t^*) &= \hat{x}_0 = e^{A t^*} 500B - x^e \\ \hat{x}(t_f) &= [0 \ 0 \ 0]^T \\ \hat{u}(t) &\in \mathcal{G} = \{\hat{u}(t) : \hat{u}(t) + u^e \geq 0, \forall t \geq 0\} \end{aligned} \quad (5.17)$$

with $Q = Q^T > 0$ and $R = R^T > 0$ are design matrices, $\hat{x}(t) = x(t) - x^e$, $\hat{u}(t) = u(t) - u^e$, $x^e = \begin{bmatrix} 1 & 1 & 1 \end{bmatrix}^T u^e$, $u^e = \left(\frac{100}{y_{NMB}^{ref}} - 1 \right)^{1/\gamma} C_{50}$, and the column-matrix A and the vector B given by

$$A = \begin{bmatrix} -\alpha k_3 & 0 & 0 \\ \alpha k_2 & -\alpha k_2 & 0 \\ 0 & \alpha k_1 & -\alpha k_1 \end{bmatrix} \quad \text{and} \quad B = \begin{bmatrix} \alpha k_3 \\ 0 \\ 0 \end{bmatrix},$$

for the fixed values of $k_1 = 1$, $k_2 = 4$, $k_3 = 10$ and $C_{50} = 3.2435$. Note that, $(x^e, u^e, c_e^e = u^e)$ is the set-point for the linear part of the NMB model (eq. 2.12) corresponding to the NMB level y_{NMB}^{ref} .

Moreover, $x(t^*) = e^{At^*} 500B$ is the state at time t^* corresponding to the administration of an initial bolus of $500 \mu\text{g/kg}$ of *atracurium*, as is usually done in clinical practice.

The cost functional in (5.17) is replaced by the moments and becomes equal to

$$\frac{1}{2} (q_1 y_{2000} + q_2 y_{0200} + q_3 y_{0020} + r y_{0002})$$

The test functions are $v(\hat{x}) = \hat{x}_1^{\beta_1} \hat{x}_2^{\beta_2} \hat{x}_3^{\beta_3}$, with the exponents given in Table 5.1.

Table 5.1: Exponents β for test function $v(\hat{x})$

β_1	β_2	β_3
1	0	0
0	1	0
0	0	1
1	1	0
1	0	1
0	1	1
2	0	0
0	2	0
0	0	2

The moment order was restricted to be $d = 2$. For moments of order up to $d = 2$, all possible combinations for the exponents are indicated in Table 5.1. The equality constraint equations corresponding to the entries in Table 5.1 are

$$\begin{aligned}
k_3 \alpha (y_{0001} - y_{1000}) + \hat{x}_1(t^*) &= 0 \\
k_2 \alpha (y_{1000} - y_{0100}) + \hat{x}_2(t^*) &= 0 \\
k_1 \alpha (y_{0100} - y_{0010}) + \hat{x}_3(t^*) &= 0 \\
k_3 \alpha (y_{0101} - y_{1100}) + k_2 \alpha (y_{2000} - y_{1100}) + \hat{x}_1(t^*) \hat{x}_2(t^*) &= 0 \\
k_3 \alpha (y_{0011} - y_{1010}) + k_1 \alpha (y_{1100} - y_{1010}) + \hat{x}_1(t^*) \hat{x}_3(t^*) &= 0 \\
k_2 \alpha (y_{1010} - y_{0110}) + k_1 \alpha (y_{0200} - y_{0110}) + \hat{x}_2(t^*) \hat{x}_3(t^*) &= 0 \\
2k_3 \alpha (y_{1001} - y_{2000}) + \hat{x}_1^2(t^*) &= 0 \\
2k_2 \alpha (y_{1100} - y_{0200}) + \hat{x}_2^2(t^*) &= 0 \\
2k_1 \alpha (y_{0110} - y_{0020}) + \hat{x}_3^2(t^*) &= 0
\end{aligned}$$

The optimal moment matrix $M_d(y^*)$ is the obtained after the optimal moments, y^* , are computed by numerical solvers, *e.g.*, CVX, Grant and Boyd (2015).

$$M^* = M_d(y^*) = \begin{bmatrix} y_{0000}^* & y_{1000}^* & y_{0100}^* & y_{0010}^* & y_{0001}^* \\ y_{1000}^* & y_{2000}^* & y_{1100}^* & y_{1010}^* & y_{1001}^* \\ y_{0100}^* & y_{1100}^* & y_{0200}^* & y_{0110}^* & y_{0101}^* \\ y_{0010}^* & y_{1010}^* & y_{0110}^* & y_{0020}^* & y_{0011}^* \\ y_{0001}^* & y_{1001}^* & y_{0101}^* & y_{0011}^* & y_{0002}^* \end{bmatrix} \geq 0$$

Finally, the feedback gains can be computed from the following system of linear equations:

$$\begin{bmatrix} M^*(2,5) \\ M^*(3,5) \\ M^*(4,5) \end{bmatrix} = \begin{bmatrix} M^*(2,2) & M^*(2,3) & M^*(2,4) \\ M^*(3,2) & M^*(3,3) & M^*(3,4) \\ M^*(4,2) & M^*(4,3) & M^*(4,4) \end{bmatrix} \begin{bmatrix} K_1 \\ K_2 \\ K_3 \end{bmatrix} \quad (5.18)$$

where $M^*(i, j)$ denotes the (i, j) entry of the matrix M^* .

In order to simulate the performance of the computed feedback control laws the bank of hundred models with parameters $\theta_i = (\alpha_i, \gamma_i)$ ($i = 1, \dots, 100$) of Appendix B was considered. The data of the case number 2 was chosen as in the previous chapter. As mentioned before, the desired NMB reference level is $y_{NMB}^{ref} = 10\%$.

The control strategy used here can be summarized by the following steps:

- First, an initial *bolus* of muscle relaxant of *atracurium* is administered;
- The patient's response is monitored to determine the recovery time instant t^* using the algorithm OLARD, Silva et al. (2009);
- After time t^* the feedback gain matrix obtained by one of the previously described design methods is used and the state feedback controller is activated.

In order to compare this approach with the one presented in Chapter 4, the following results were obtained using the same scenarios considered in the that chapter. First, we compare the performance of a controller designed with $\alpha = \alpha_i$ and $\gamma = \gamma_i$ with a controller designed with $\alpha = \bar{\alpha}$ and $\gamma = \gamma_i$, $i \in \{1, \dots, 100\}$. The data set chosen corresponds to the patient $i = 2$ in the database presented in Appendix B.

Scenario 1: Results obtained using α_2 and γ_2 to design the controller:

The next results were obtained using $\alpha = \alpha_2 = 0.0412$ and $\gamma = \gamma_2 = 2.9740$ in the OCP formulation (5.17). For these values of parameters the state vector at $t = t^* = 28.7 \text{ min}$ is given by,

$$x(t^*) = \begin{bmatrix} 0.0019 \\ 1.3215 \\ 9.1216 \end{bmatrix} \quad (5.19)$$

We also considered that $Q = C^T C$ and $R = 1$, where $C = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix}$ as in (2.12). For this data set, the optimal moment matrix obtained by the solver, CVX Grant and Boyd (2015), minimizing $y_{0020} + y_{0002}$ subject to the inequality constraints and $M_d(y) \geq 0$, $M_d(gy) \geq 0$ is

$$M^* = M_d(y^*) = 10^3 \begin{bmatrix} 246.49 & -0.0038 & -0.0041 & 0.2255 & -0.0038 \\ -0.0038 & 0.0219 & 0.0113 & -0.1383 & 0.0219 \\ 0.0042 & 0.0113 & 0.0162 & -0.0488 & 0.0071 \\ 0.2255 & -0.1383 & -0.0488 & 0.9607 & -0.1533 \\ -0.0038 & 0.0218 & 0.0071 & -0.1533 & 0.0245 \end{bmatrix},$$

and the feedback gains can be computed from the following system of linear equations:

$$\begin{bmatrix} M^*(2,5) \\ M^*(3,5) \\ M^*(4,5) \end{bmatrix} = \begin{bmatrix} M^*(2,2) & M^*(2,3) & M^*(2,4) \\ M^*(3,2) & M^*(3,3) & M^*(3,4) \\ M^*(4,2) & M^*(4,3) & M^*(4,4) \end{bmatrix} \begin{bmatrix} K_1 \\ K_2 \\ K_3 \end{bmatrix} \quad (5.20)$$

yielding

$$K_{LMI} = \begin{bmatrix} -0.0122 & -0.0447 & -0.1636 \end{bmatrix}$$

Figure 5.1 shows the simulation of the NMB level response. As can be seen in Figure 5.1, the control input $u(t)$ is always non-negative. It can be shown that, due to the compartmental structure of the system, this implies that also the state components $x = \hat{x} + x^{ref}$ are non-negative. Therefore, the original problem constraints are indeed satisfied. One can also observe that the NMB level settles to the set-point of 10%.

Scenario 2: Results obtained using $\bar{\alpha}$ and γ_2 to design the controller:

Here, the controller was designed using $\alpha = \bar{\alpha} = 0.0382$ and $\gamma = \gamma_2 = 2.9740$ in the OCP formulation 5.17. The matrices of the cost functional were assumed to be $Q = C^T C$ and $R = 1$. For this data set, the optimal moment matrix obtained by the solver CVX, Grant and

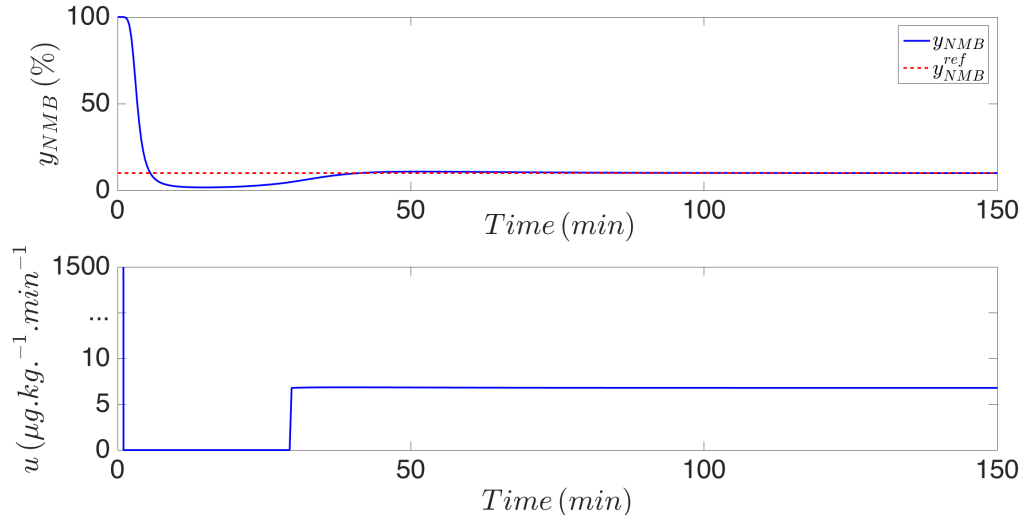


Figure 5.1: Simulation of the NMB level response (upper plot) using the state-feedback control (bottom plot) given by the moment relaxation design method.

Boyd (2015), minimizing $y_{0020} + y_{0002}$ subject to the inequality constraints and $M_d(y) \geq 0$, $M_d(gy) \geq 0$ is

$$M^* = M_d(y^*) = 10^3 \begin{bmatrix} 268.02 & -0.0035 & 0.0051 & 0.2439 & -0.0035 \\ -0.0035 & 0.0236 & 0.0123 & -0.1492 & 0.0236 \\ 0.0051 & 0.0122 & 0.0179 & -0.0527 & 0.0077 \\ 0.2439 & -0.1492 & -0.0527 & 1.0364 & -0.1654 \\ -0.0035 & 0.0236 & 0.0077 & -0.1654 & 0.0264 \end{bmatrix},$$

and the feedback gains can be computed from the following system of linear equations:

$$\begin{bmatrix} M^*(2,5) \\ M^*(3,5) \\ M^*(4,5) \end{bmatrix} = \begin{bmatrix} M^*(2,2) & M^*(2,3) & M^*(2,4) \\ M^*(3,2) & M^*(3,3) & M^*(3,4) \\ M^*(4,2) & M^*(4,3) & M^*(4,4) \end{bmatrix} \begin{bmatrix} K_1 \\ K_2 \\ K_3 \end{bmatrix} \quad (5.21)$$

yielding

$$K_{LMI} = \begin{bmatrix} -0.0121 & -0.0447 & -0.1636 \end{bmatrix}.$$

Figure 5.2 shows a comparison between the results obtained under the conditions of scenarios 1 and 2. Again, the control input $u(t)$ is always non-negative and, consequently, the state

components $x = \hat{x} + x^{ref}$ are non-negative. Therefore, the original problem constraints are indeed satisfied. One can also observe that the NMB level settles to the set-point of 10%.

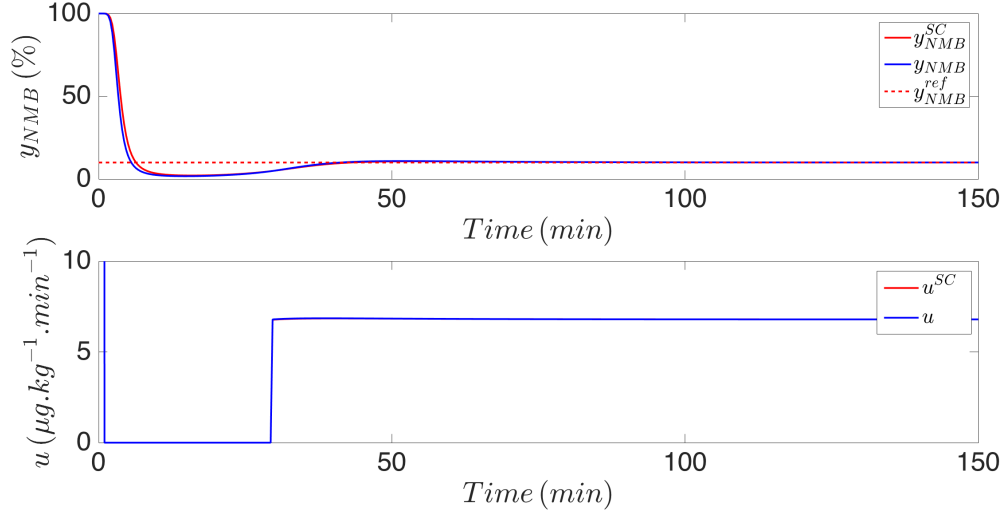


Figure 5.2: Simulation of the NMB level response (upper plot) using the state-feedback control (bottom plot) given by the moment relaxation design method, both for the scenarios 1 (u and y_{NMB}) and 2 (u^{SC} and y_{NMB}^{SC})

Results obtained using the parameters identified by the EKF

Finally, Similarly to what was done for the previously proposed positive control law, here we combine the control with the parameter identification performed by the EKF algorithm. For that end, the real case number of 8 of Appendix C was used as in the previous chapter. For this purpose the patient's data (γ) identified by the EKF algorithm identified at the time instant $t^* = 31 \text{ min}$ is $\hat{\gamma} = 2.558$. The controller was thus designed using $\alpha = \bar{\alpha} = 0.0382$ and $\gamma = \hat{\gamma}(t^*) = 2.558$ in the OCP formulation (5.17). Again, the matrices of the cost functional were assumed to be $Q = C^T C$ and $R = 1$. The optimal moment matrix obtained by the solver, CVX Grant and Boyd (2015), minimizing $y_{0020} + y_{0002}$ subject to the inequality constraints and $M_d(y) \geq 0$, $M_d(gy) \geq 0$ is

$$M^* = M_d(y^*) = 10^3 \begin{bmatrix} 262.64 & -0.0045 & 0.0041 & 0.2429 & -0.0045 \\ -0.0045 & 0.0236 & 0.0122 & -0.1492 & 0.0236 \\ 0.0041 & 0.0122 & 0.0179 & -0.0527 & 0.0077 \\ 0.2429 & -0.1492 & -0.0527 & 1.0364 & -0.1653 \\ -0.0045 & 0.0236 & 0.0077 & -0.1654 & 0.0264 \end{bmatrix}$$

And the feedback gains can be computed from the following system of linear equations:

$$\begin{bmatrix} M^*(2,5) \\ M^*(3,5) \\ M^*(4,5) \end{bmatrix} = \begin{bmatrix} M^*(2,2) & M^*(2,3) & M^*(2,4) \\ M^*(3,2) & M^*(3,3) & M^*(3,4) \\ M^*(4,2) & M^*(4,3) & M^*(4,4) \end{bmatrix} \begin{bmatrix} K_1 \\ K_2 \\ K_3 \end{bmatrix} \quad (5.22)$$

yielding

$$K_{LMI} = \begin{bmatrix} -0.0123 & -0.0447 & 0.1636 \end{bmatrix}$$

Figure 5.3 shows the simulation of the NMB level response. Again, the control input $u(t)$ is always non-negative which implies that also the state components $x = \hat{x} + x^{ref}$ are non-negative. Therefore, the original problem constraints are indeed satisfied. One can also observe that the NMB level settles to the set-point of 10%.

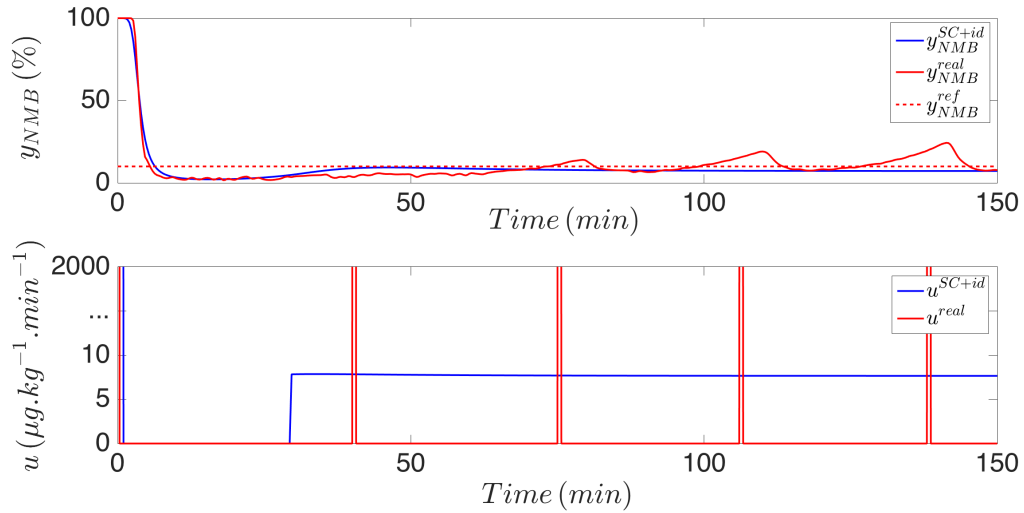


Figure 5.3: Simulation of the NMB level response (upper plot) using the state-feedback control (bottom plot) given by the moment relaxation design method. y_{NMB}^{SC+id} represents the NMB level obtained using the state-feedback control with parameter identification, y_{NMB}^{real} is the real NMB signal obtained during a general surgery and y_{NMB}^{ref} is the reference NMB level.

Similarly to what was done to evaluate the control approach for the NMB level in Chapter 4, Figure 5.4 shows the amount of drug given by the controller compared with the real amount of drug administered. As it is possible to see the amount of drug given by the controller is higher than the amount of drug given by the clinicians. However, as it is possible to see in Figure 5.5, the control approach is much better in stabilizing the NMB level near of the NMB reference level.

The relationship between the amount of drug administered and the NMB level is again

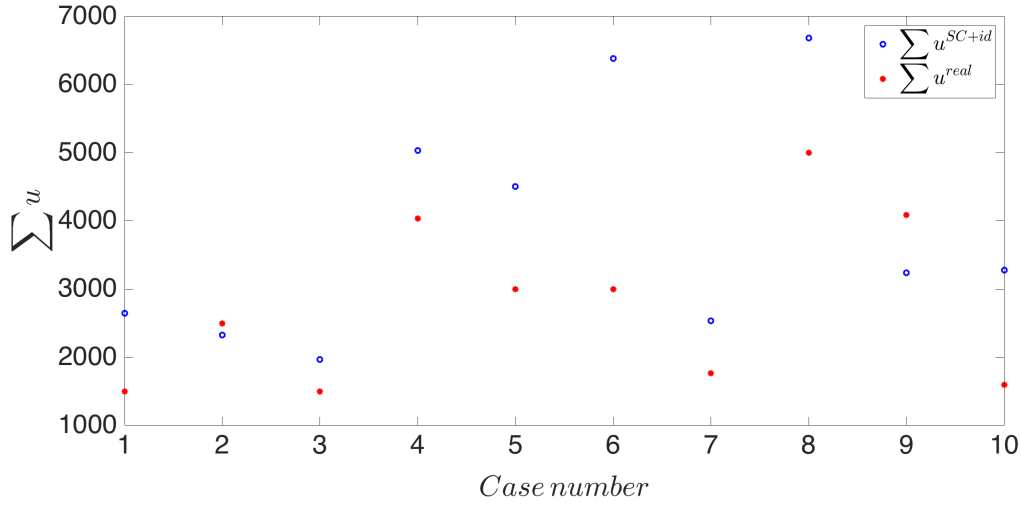


Figure 5.4: Total amount of *atracurium* administered during the surgery (red star) and the total amount determined by the control scheme (blue bullet). $\sum u^{SC+id}$ is the total amount of *atracurium* administered using the state-feedback control with parameter identification and $\sum u^{SC}$ is the total amount of *atracurium* administered to the 10 real cases of the database of Appendix C

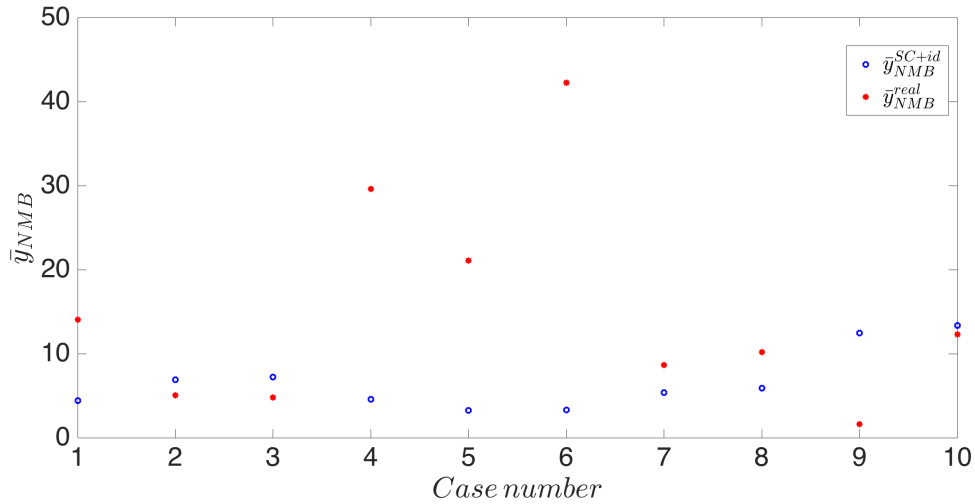


Figure 5.5: Mean of the real NMB level between the time instants t_i and t_f (red star) and mean of the simulated NMB level in the same time interval (blue bullet) for 10 cases of the database of Appendix C. t_i is the first time instant where the response is lower than 10% and t_f is the time instant when the surgery ends. $\bar{y}_{NMB}^{SC+id}$ is the mean of the NMB level obtained using the state-feedback control with parameter identification in that time interval and $\bar{y}_{NMB}^{real}$ is the mean of the real NMB level for the 10 cases of the database of Appendix C.

evaluated by the cost functional,

$$J_i = \frac{1}{n} \sum_{t=0}^n \left(\left(y_{NMB}^{ref} - y_{NMB}(t) \right)^2 + \kappa u^2(t) \right), \quad i = 1, \dots, 10 \quad (5.23)$$

with $\kappa = 1$. Although the amount of drug given by the controller is higher than the real case, the cost functional for the control approach is lower than the real case. So, we can conclude that the trade-off between the amount of drug and the quality of tracking the desired NMB level is compensated in our control approach. This result is corroborated by the results depicted in Figure 5.6

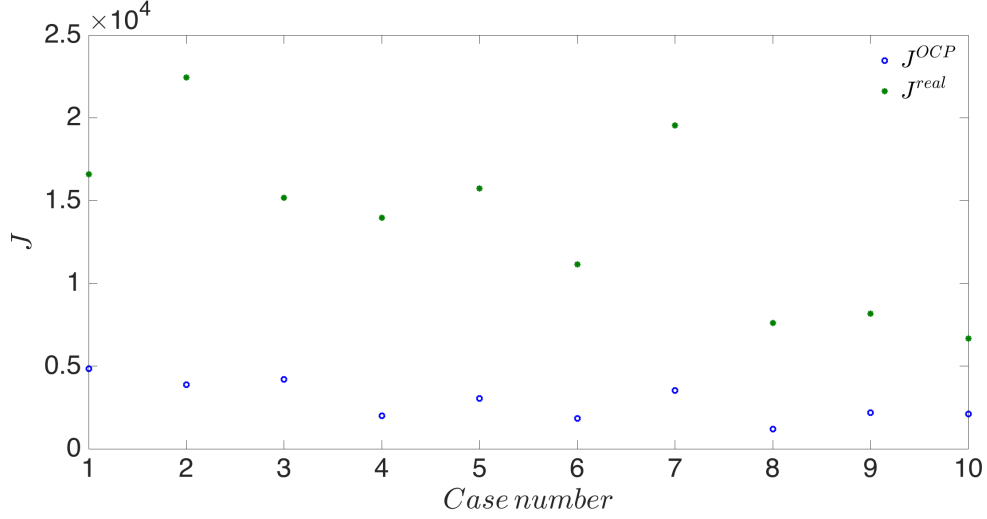


Figure 5.6: Cost value obtained for the real cases (blue bullet) and the cost value obtained for the control scheme (red star) for 10 cases of the database of Appendix C. J^{SC+id} is the cost value for the signals obtained using the state-feedback control with parameter identification and J^{SC+id} is the cost value obtained using the real signals collected in the clinical practice.

5.2 Optimal control for remifentanyl and propofol - BIS case

In this section an optimal control problem is formulated in order to track a desired BIS level. Each drug will be controlled separately, *i.e.*, an OCP will be formulated to design a controller for *propofol* dose and another one to control the *remifentanyl* dose.

The optimal control problem associated to the *propofol* dynamics is formulated as,

$$\begin{aligned}
 \min_{\hat{u}^P(t), t_f} \quad & J(\hat{x}^P(t), \hat{u}^P(t)) = \frac{1}{2} \int_{t^*}^{t_f} \underbrace{(\hat{x}^P)^T Q \hat{x}^P(t) + (\hat{u}^P)^T R \hat{u}^P(t)}_{h^P(\hat{x}^P(t), \hat{u}^P(t))} dt \\
 \text{s.t.} \quad & \hat{\dot{x}}^P(t) = \underbrace{A^P \hat{x}^P(t) + B^P \hat{u}^P(t)}_{f^P(\hat{x}^P(t), \hat{u}^P(t))} \\
 & \hat{x}^P(t^*) = -(\hat{x}^R)^e \\
 & \hat{x}^P(t_f) = [0 \ 0 \ 0]^T \\
 & \hat{u}^P(t) \in \mathcal{G}^P = \left\{ \hat{u}^P(t) : \hat{u}^P(t) + (u^P)^e \geq 0, \forall t \geq 0 \right\}
 \end{aligned} \tag{5.24}$$

with $\hat{x}^P(t) = x^P(t) - (x^P)^e$, $\hat{u}^P = u^P - (u^P)^e$, $\hat{x}_0^P = -(x^P)^e$, the matrix A^P and the column-matrix B^P are defined by,

$$A^P = \begin{bmatrix} -\xi d_3 & 0 & 0 \\ \xi d_2 & -\xi d_2 & 0 \\ 0 & \xi d_1 & -\xi d_1 \end{bmatrix}, \quad B^P = \begin{bmatrix} \xi d_3 \\ 0 \\ 0 \end{bmatrix}, \quad (5.25)$$

$d_1 = 1$, $d_2 = 9$ and $d_3 = 10$. As mentioned in Section 4.1.2, the vector $(x^P)^e$ has all entries equal to $(u^P)^e$, i.e.,

$$(x^P)^e = \begin{bmatrix} 1 & 1 & 1 \end{bmatrix}^T (u^P)^e \quad \text{and} \quad (u^P)^e = \frac{\rho z^e}{\frac{1}{C_{50}^P} m \rho + \frac{1}{C_{50}^R}} \quad (5.26)$$

where $C_{50}^P = 10 \text{ mg.ml}^{-1}$ and $C_{50}^R = 0.1 \text{ mg.ml}^{-1}$, z^e is the desired BIS reference level and ρ is to be fixed.

For the same reason as mentioned before, the moment order was restricted to be $d = 2$ and all possible combinations for the exponents of the test functions, $v(\hat{x}^P) = \hat{x}_1^{\beta_1} \hat{x}_2^{\beta_2} \hat{x}_3^{\beta_3}$, are indicated in Table 5.1. The equality constraint equations corresponding to the entries of the Table 5.1 for the *propofol* model are,

$$\begin{aligned} d_3 \xi (y_{0001}^P - y_{1000}^P) + \hat{x}_1^P(t^*) &= 0 \\ d_2 \xi (y_{1000}^P - y_{0100}^P) + \hat{x}_2^P(t^*) &= 0 \\ d_1 \xi (y_{0100}^P - y_{0010}^P) + \hat{x}_3^P(t^*) &= 0 \\ d_3 \xi (y_{0101}^P - y_{1100}^P) + k_2 \xi (y_{2000}^P - y_{1100}^P) + \hat{x}_1^P(t^*) \hat{x}_2^P(t^*) &= 0 \\ d_3 \xi (y_{0011}^P - y_{1010}^P) + k_1 \xi (y_{1100}^P - y_{1010}^P) + \hat{x}_1^P(t^*) \hat{x}_3^P(t^*) &= 0 \\ d_2 \xi (y_{1010}^P - y_{0110}^P) + k_1 \xi (y_{0200}^P - y_{0110}^P) + \hat{x}_2^P(t^*) \hat{x}_3^P(t^*) &= 0 \\ 2d_3 \xi (y_{1001}^P - y_{2000}^P) + (\hat{x}_1^P)^2(t^*) &= 0 \\ 2d_2 \xi (y_{1100}^P - y_{0200}^P) + (\hat{x}_2^P)^2(t^*) &= 0 \\ 2d_1 \xi (y_{0110}^P - y_{0020}^P) + (\hat{x}_3^P)^2(t^*) &= 0 \end{aligned}$$

The optimal moment matrix $M_d(y^{P*})$ is the obtained after the optimal moments, y^{P*} , are computed by numerical solvers, e.g., CVX, Grant and Boyd (2015).

$$M^{P*} = M_d(y^{P*}) = \begin{bmatrix} y_{0000}^P & y_{1000}^P & y_{0100}^P & y_{0010}^P & y_{0001}^P \\ y_{1000}^P & y_{2000}^P & y_{1100}^P & y_{1010}^P & y_{1001}^P \\ y_{0100}^P & y_{1100}^P & y_{0200}^P & y_{0110}^P & y_{0101}^P \\ y_{0010}^P & y_{1010}^P & y_{0110}^P & y_{0020}^P & y_{0011}^P \\ y_{0001}^P & y_{1001}^P & y_{0101}^P & y_{0011}^P & y_{0002}^P \end{bmatrix} \geq 0$$

Finally, the feedback gains can be computed from the following system of linear equations:

$$\begin{bmatrix} M^{P*}(2,5) \\ M^{P*}(3,5) \\ M^{P*}(4,5) \end{bmatrix} = \begin{bmatrix} M^{P*}(2,2) & M^{P*}(2,3) & M^{P*}(2,4) \\ M^{P*}(3,2) & M^{P*}(3,3) & M^{P*}(3,4) \\ M^{P*}(4,2) & M^{P*}(4,3) & M^{P*}(4,4) \end{bmatrix} \begin{bmatrix} K_1^P \\ K_2^P \\ K_3^P \end{bmatrix} \quad (5.27)$$

The OCP formulated to find the *remifentanyl* dose has the following structure,

$$\begin{aligned} \min_{\hat{x}^R(t), \hat{u}^R(t)} J(\hat{x}^R(t), \hat{u}^R(t)) &= \frac{1}{2} \int_{t^*}^{t_f} \underbrace{(\hat{x}^R)^T Q \hat{x}^R(t) + (\hat{u}^R)^T R \hat{u}^R(t)}_{h^R(\hat{x}^R(t), \hat{u}^R(t))} dt \\ \text{s.t. } \hat{x}^R(t) &= \underbrace{A^R \hat{x}^R(t) + B^R \hat{u}^R(t)}_{f^R(\hat{x}^R(t), \hat{u}^R(t))} \\ \hat{x}^R(t^*) &= -(x^R)^e \\ \hat{x}^R(t_f) &= [0 \ 0 \ 0]^T \\ \hat{u}^R(t) &\in \mathcal{G}^R = \left\{ \hat{u}^R(t) : \hat{u}^R(t) + (u^R)^e \geq 0, \forall t \geq 0 \right\} \end{aligned} \quad (5.28)$$

with $\hat{x}^R(t) = x^R(t) - (x^R)^e$, $\hat{u}^R = u^R - (u^R)^e$, $\hat{x}_0^R = -(x^R)^e$, the matrix A^R and the vector B^R are defined by,

$$A^R = \begin{bmatrix} -\eta l_3 & 0 & 0 \\ \eta l_2 & -\eta l_2 & 0 \\ 0 & \eta l_1 & -\eta l_1 \end{bmatrix} \text{ and } B^R = \begin{bmatrix} \eta l_3 \\ 0 \\ 0 \end{bmatrix}, \quad (5.29)$$

$l_1 = 1$, $l_2 = 2$ and $l_3 = 3$, and the vector $(x^P)^e$ is equal to $(x^P)^e \begin{bmatrix} 1 & 1 & 1 \end{bmatrix}^T$ with

$$(u^R)^e = \frac{z^e}{\frac{1}{C_{50}^P} m \rho + \frac{1}{C_{50}^R}} \quad (5.30)$$

Again and for the same reason as before, the moment order was restricted to be $d = 2$ and all possible combinations for the exponents of the test functions, $v(\hat{x}^R) = \hat{x}_1^{R\beta_1} \hat{x}_2^{R\beta_2} \hat{x}_3^{R\beta_3}$, are indicated in Table 5.1. The equality constraint equations corresponding to the entries of the Table 5.1 for the *remifentanyl* model are,

$$\begin{aligned}
l_3 \eta (y_{0001}^R - y_{1000}^R) + \hat{x}_1^R(t^*) &= 0 \\
l_2 \eta (y_{1000}^R - y_{0100}^R) + \hat{x}_2^R(t^*) &= 0 \\
l_1 \eta (y_{0100}^R - y_{0010}^R) + \hat{x}_3^R(t^*) &= 0 \\
l_3 \eta (y_{0101}^R - y_{1100}^R) + l_2 \eta (y_{2000}^R - y_{1100}^R) + \hat{x}_1^R(t^*) \hat{x}_2^R(t^*) &= 0 \\
l_3 \eta (y_{0011}^R - y_{1010}^R) + l_1 \eta (y_{1100}^R - y_{1010}^R) + \hat{x}_1^R(t^*) \hat{x}_3^R(t^*) &= 0 \\
l_2 \eta (y_{1010}^R - y_{0110}^R) + l_1 \eta (y_{0200}^R - y_{0110}^R) + \hat{x}_2^R(t^*) \hat{x}_3^R(t^*) &= 0 \\
2l_3 \eta (y_{1001}^R - y_{2000}^R) + (\hat{x}_1^R)^2(t^*) &= 0 \\
2l_2 \eta (y_{1100}^R - y_{0200}^R) + (\hat{x}_2^R)^2(t^*) &= 0 \\
2l_1 \eta (y_{0110}^R - y_{0020}^R) + (\hat{x}_3^R)^2(t^*) &= 0
\end{aligned}$$

The optimal moment matrix $M_d(y^{R*})$ is the obtained after the optimal moments, y^{R*} , are computed by numerical solvers, e.g., CVX, Grant and Boyd (2015).

$$M^{R*} = M_d(y^{R*}) = \begin{bmatrix} y_{0000}^{R*} & y_{1000}^{R*} & y_{0100}^{R*} & y_{0010}^{R*} & y_{0001}^{R*} \\ y_{1000}^{R*} & y_{2000}^{R*} & y_{1100}^{R*} & y_{1010}^{R*} & y_{1001}^{R*} \\ y_{0100}^{R*} & y_{1100}^{R*} & y_{0200}^{R*} & y_{0110}^{R*} & y_{0101}^{R*} \\ y_{0010}^{R*} & y_{1010}^{R*} & y_{0110}^{R*} & y_{0020}^{R*} & y_{0011}^{R*} \\ y_{0001}^{R*} & y_{1001}^{R*} & y_{0101}^{R*} & y_{0011}^{R*} & y_{0002}^{R*} \end{bmatrix} \geq 0$$

Finally, the feedback gains can be computed from the following system of linear equations:

$$\begin{bmatrix} M^{R*}(2,5) \\ M^{R*}(3,5) \\ M^{R*}(4,5) \end{bmatrix} = \begin{bmatrix} M^{R*}(2,2) & M^{R*}(2,3) & M^{R*}(2,4) \\ M^{R*}(3,2) & M^{R*}(3,3) & M^{R*}(3,4) \\ M^{R*}(4,2) & M^{R*}(4,3) & M^{R*}(4,4) \end{bmatrix} \begin{bmatrix} K_1^R \\ K_2^R \\ K_3^R \end{bmatrix} \quad (5.31)$$

In order to compare this approach with the one presented in Chapter 4 for the BIS case, the following results were obtained using the same scenarios considered in the previous chapter.

First, we compare the performance of a controller designed with $\xi = \xi_i$, $\eta = \eta_i$, $m = m_i$ and $\zeta = \zeta_i$ with a controller designed with $\xi = \bar{\xi}$, $\eta = \bar{\eta}$, $m = m_i$ and $\zeta = \zeta_i$, $i \in \{1, \dots, 18\}$.

The data set chosen corresponds to the patient number $i = 8$ of the database presented in Appendix E.

In a second stage, a comparison will be made with the performance obtained of the patient number 18 when the simplified control law of Chapter 4 is combined with the identification method.

Scenario 1: Results obtained using ξ_8 , η_8 , m_8 and ζ_8 to design the controller:

The next results were obtained using $\xi = \xi_8 = 0.0860$, $\eta = \eta_8 = 0.0212$, $m = m_8 = 1.4203$ and $\zeta = \zeta_8 = 0.9780$ in the OCP formulations (5.24) and (5.28).

We considered that $Q = 10 \times C^T C$, $R = 10$ and the value ρ in equation (5.26) was taken to be equal to 500. For this data set, the optimal feedback gains for the *propofol* and *remifentanyl* models obtained by the solver, CVX Grant and Boyd (2015), are:

$$\begin{aligned} K_{LMI}^P &= \begin{bmatrix} -0.0320 & -0.0407 & -0.3396 \end{bmatrix} \\ K_{LMI}^R &= \begin{bmatrix} 0.1601 & 0.0702 & -0.5809 \end{bmatrix}. \end{aligned}$$

Figure 5.7 shows the simulation of the BIS level response obtained using a controller given by the solution of the OCP formulations (5.24) and (5.28). As can be seen in Figure 5.7, the control inputs $u^P(t)$ and $u^R(t)$ are always non-negative. It can be shown that, due to the structure of the system, this implies that also the state components $x^P = \hat{x}^P + x^{refP}$ and $x^R = \hat{x}^R + x^{refR}$ are non-negative. Therefore, the original problem constraints are indeed satisfied.

Scenario 2: Results obtained using $\bar{\xi}$, $\bar{\eta}$, m_8 and ζ_8 to design the controller:

The next results were obtained using $\xi = \bar{\xi} = 0.0759$, $\eta = \bar{\eta} = 0.5825$, $m = m_8 = 1.4203$ and $\zeta = \zeta_8 = 0.9780$ in the OCP formulations (5.24) and (5.28). Again, the matrices of the cost functional were assumed to be equal $Q = 10 \times C^T C$, $R = 10$ and the value ρ in equation (5.26) was taken to be equal to 500. For this data set, the optimal feedback gains for the *propofol* and *remifentanyl* models obtained by the solver CVX, Grant and Boyd (2015), are:

$$\begin{aligned} K_{LMI}^P &= \begin{bmatrix} -0.0318 & -0.0408 & -0.3396 \end{bmatrix} \\ K_{LMI}^R &= \begin{bmatrix} 0.8299 & 0.1813 & -0.1372 \end{bmatrix} \end{aligned}$$

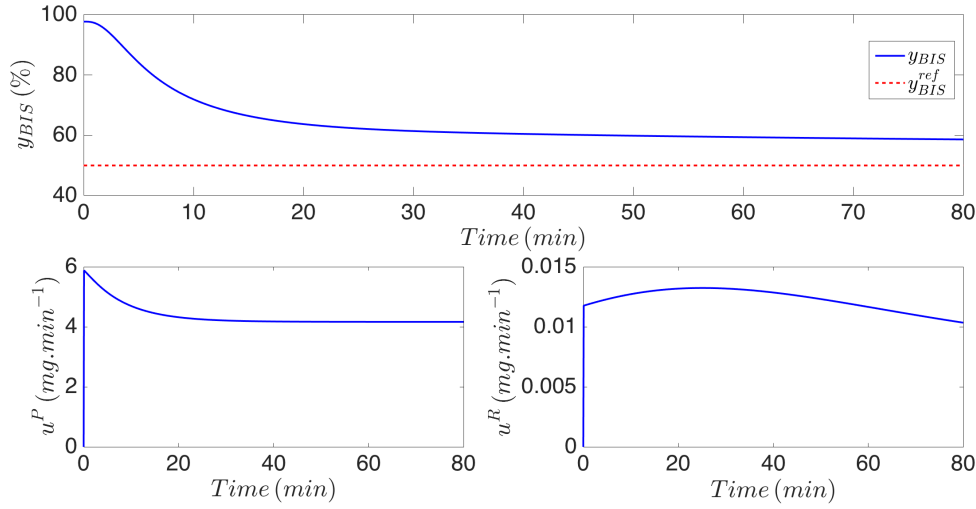


Figure 5.7: Simulation of the BIS level response, y_{BIS} , (upper plot) using the state-feedback control (bottom plot) given by the moment relaxation method designed with $\xi = \xi_8 = 0.0860$, $\eta = \eta_8 = 0.0212$, $m = m_8 = 1.4203$ and $\zeta = \zeta_8 = 0.9780$.

Figure 5.8 shows the simulation of the BIS level response taking into account the previous feedback gains. As can be seen in Figure 5.8, the control input signals $u^P(t)$ and $u^R(t)$ are always non-negative and, consequently, the original problem constraints are indeed satisfied.

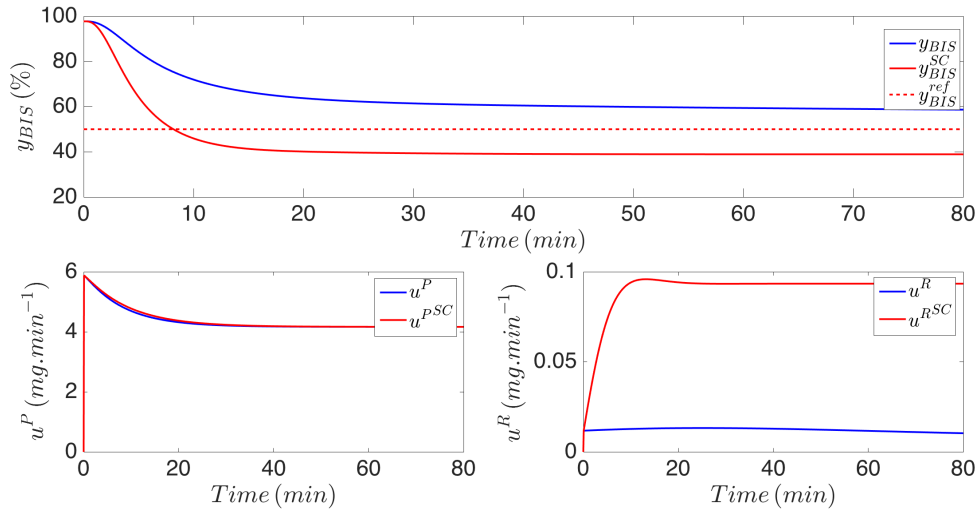


Figure 5.8: Comparison between the BIS level response, y_{BIS} , (upper plot) using the state-feedback control, u , (bottom plot) given by the moment relaxation method designed with $\xi = \xi_8 = 0.0860$, $\eta = \eta_8 = 0.0212$, $m = m_8 = 1.4203$ and $\zeta = \zeta_8 = 0.9780$ and the BIS level y_{BIS}^{SC} using the simplified state-feedback control u^{SC} , *i.e.*, using the state-feedback control designed with $\xi = \bar{\xi} = 0.0759$, $\eta = \bar{\eta} = 0.5825$, $m = m_8 = 1.4203$ and $\zeta = \zeta_8 = 0.9780$.

Results obtained using the parameters identified by the EKF

Finally, the control approach is combined with the parameter identification performed by the EKF algorithm. The real case number 18 of Appendix E was used as in the previous chapter. For this patient's data the EKF algorithm identified m at the time instant $t^* = 4 \text{ min}$ as 1.998 and ζ as 1.001. The matrices of the cost functional were assumed to be equal $Q = 10 \times C^T C$, $R = 10$ and the value ρ in equation (5.26) was taken to be equal to 500. The optimal feedback gains for the *propofol* and *remifentanyl* models obtained by the solver CVX, Grant and Boyd (2015), are:

$$\begin{aligned} K_{LMI}^P &= \begin{bmatrix} -0.0326 & -0.0404 & -0.3397 \end{bmatrix} \\ K_{LMI}^R &= \begin{bmatrix} 1.3064 & -0.3480 & -0.0883 \end{bmatrix} \end{aligned}$$

Figure 5.9 shows the simulation of the BIS level response using the proposed control scheme in this chapter. As can be seen in Figure 5.9, the control problem constraints, *i.e.*, the positivity of state and input signals, are satisfied.

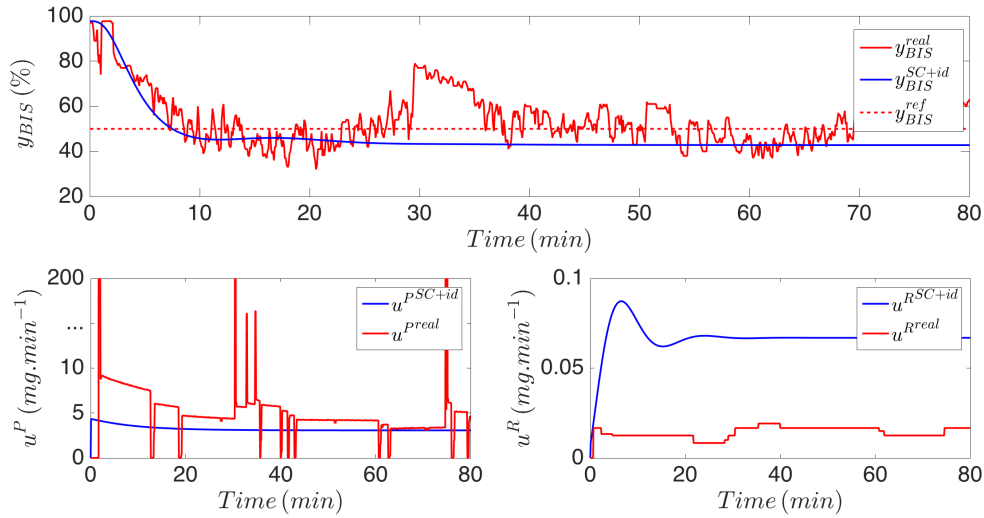


Figure 5.9: Simulation of the BIS level response (upper plot) using the state-feedback control (bottom plot) given by the moment relaxation method designed using $\xi = \bar{\xi} = 0.0759$, $\eta = \bar{\eta} = 0.5825$, $m = m(t^*) = 1.998$ and $\zeta = \zeta(t^*) = 1.001$. $\sum u^{PSC+id}$ and $\sum u^{Preal}$ represent the *propofol* doses obtained by the simplified state-feedback controllers with parameter identification and the ones obtained for the real cases (in clinical environment), respectively, and $\sum u^{RSC+id}$ and $\sum u^{Rreal}$ represent the *remifentanyl* doses obtained by the simplified state-feedback controllers with parameter identification and the ones obtained for the real cases (in clinical environment), respectively.

Figure 5.10 shows the amount of drug given by the last controller compared with the real amount of drug administered.

As it is possible to see the amount of *propofol* given by the controller is lower than the amount of drug given by the clinicians and the amount of *remifentanyl* given by the controller is higher than the amount of drug given by the clinicians. As it is possible to see in Figure 5.11, the control approach stabilizes the BIS level near 40%, which is not close to the suitable BIS reference level 50%. So, this approach control does not achieve the expected desired value, but it still yields a BIS value that falls in a clinical admissible range, Gan et al. (1997).

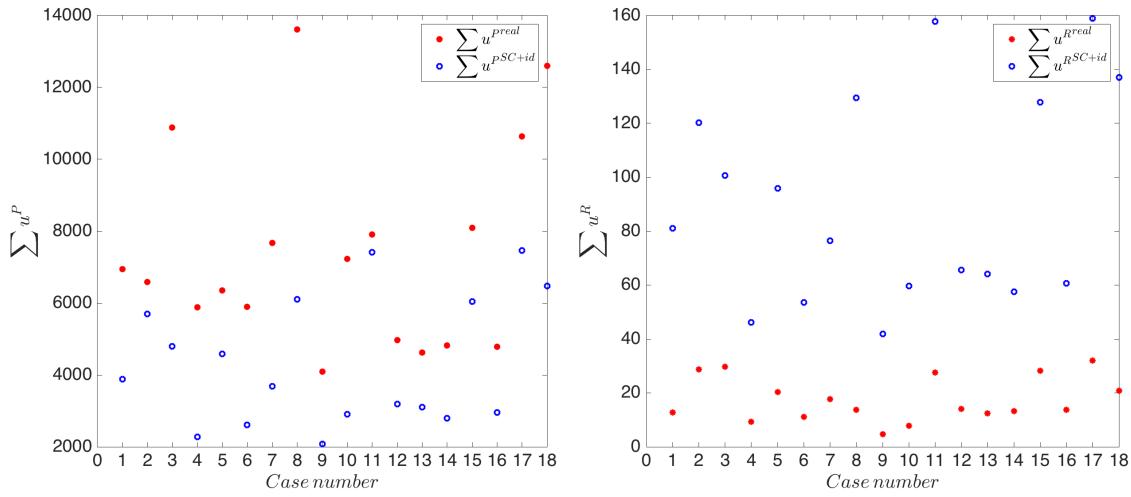


Figure 5.10: Total amount of *propofol* and of *remifentanyl* administered during the surgery (red star) and the total amount determined by the control scheme (blue bullet). $\sum u^{pSC+id}$ and $\sum u^{preal}$ represent the *propofol* doses obtained by the simplified controllers with parameter identification and the ones obtained for the real cases (in clinical environment), respectively, and $\sum u^{RSC+id}$ and $\sum u^{Rreal}$ represent the *remifentanyl* doses obtained by the simplified state-feedback controllers with parameter identification and the ones obtained for the real cases (in clinical environment), respectively.

The relationship between the amount of drug administered and the BIS level is computed by the following cost functional as in the previous chapter,

$$J_i = \frac{1}{n} \sum_{t=0}^n \left(\left(y_{BIS}^{ref} - y_{BIS}(t) \right)^2 + \kappa \left(u^P(t) + u^R(t) \right)^2 \right), \quad i = 1, \dots, 8 \quad (5.32)$$

Similarly to the other results, the cost functional for the proposed control is lower than the real case as it is possible to see in Figure 5.12. So, we can conclude that the use of a controller scheme is profitable.

In this chapter, control laws were designed that correspond to the solution of optimal control problems. An optimal control problem was formulated for the control of the amount of muscle relaxant that should be administered to achieve the NMB reference level. For the BIS case, with the aim of controlling the amounts of hypnotic and analgesic, two optimal

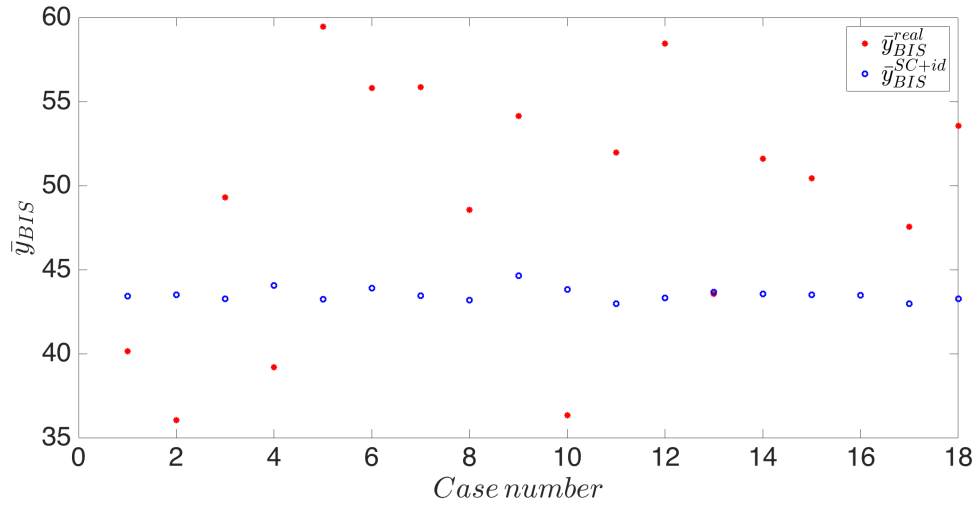


Figure 5.11: Mean of the real BIS level between the time instants t_i and t_f (red star) and mean of the simulated NMB level in the same time interval (blue bullet). t_i is the first time instant where the response is lower than 50% and t_f is the time instant when the surgery ends. $\bar{y}_{BIS}^{SC+id}$ represents the mean of the BIS level between in the time interval $[t_i, t_f]$ obtained by the simplified state-feedback control with parameter identification and $\bar{y}_{BIS}^{real}$ represents the mean of the real BIS level between in the same time interval.

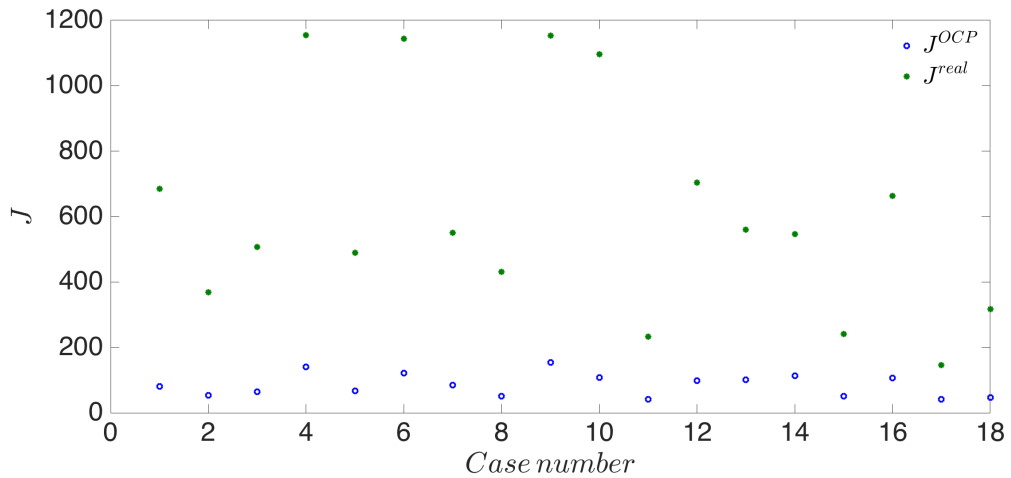


Figure 5.12: Cost value obtained for the real cases (blue bullet) and the cost value obtained for the control scheme (red star). J^{SC+id} represents the cost value obtained using the signals obtained by the simplified state-feedback control with parameter identification and J^{real} represents the cost value obtained using the real signals obtained during the general surgery.

control problems were considered. In both cases, the problems were solved by first replacing the original variables by their moments up to a certain order. Then, the moments were computed by the solver CVX, in order to obtain the feedback gains of the control law. The performance of this control approach was analyzed by means of a cost functional which involves both the amount of used drug and the reference tracking error. It turns out that the

cost of our automatic controller is much lower than the one of manual drug administration used in the real practice.

6

Conclusions

This thesis focuses on the analyze of the feedback controllers of positive linear systems with a static nonlinearity at the output in the context of anesthesia. The controllers presented in this thesis were design based on simplified models, and consequently, present a simplified structure. More concretely, two distinct control approaches were analyzed. One of the control approach (presented in Chapter 4) consists in stabilizing what was called (with some abuse of language) the "total system mass" into a desired reference value considering a positive control law designed for compartmental system. The advantage of the first control scheme is the possibility of readjusting the control by adjusting of the reference level during the process. The other control scheme (presented in Chapter 5) is obtained by solving an optimal control problem. The main advantage of this control law is the possibility of choosing the optimality criterion taking into account the physiological patient condition.

Both approaches were combined with an algorithm for parameter identification in order to be in accordance to what should happen in the real environment. The identification method used was the Extended Kalman Filter. This algorithm was applied to identify the patient-dependent parameters of the nonlinearity in the models.

The two aforementioned control approaches were applied to control two important components of anesthesia: the neuromuscular blockade (NMB), and the depth of anesthesia which is monitored by the bispectral level (BIS).

A comparison between the results obtained in Chapters 4 and 5 for the control of the NMB level and BIS level is made then.

6.1 Comparison of the NMB case results

This section presents a comparison of the results obtained for the NMB case. For this purpose, the cost function presented in Chapter 4 is used to compare the performance of the controller approaches (with parameter identification).

Recall that the cost function is given by the following equation:

$$J = \frac{1}{n} \sum_{t=0}^n \left(\left(y_{NMB}^{ref} - y_{NMB}(t) \right)^2 + \kappa u^2(t) \right), \quad (6.1)$$

with $\kappa = 1$.

This cost functional was computed using the signals obtained by the two different approaches (of Chapters 4 and 5, respectively) and using the real signals collected during the actual surgeries. In Figure 6.1 shows the values obtained using the simplified positive control law, J^{PCL} , the ones obtained by using the control given by solving the optimal control problem, J^{OCP} , and the cost functional obtained using the real signals, J^{real} . As it is possible to see, the performance of the second controller is better than the performance of the compartmental control law.

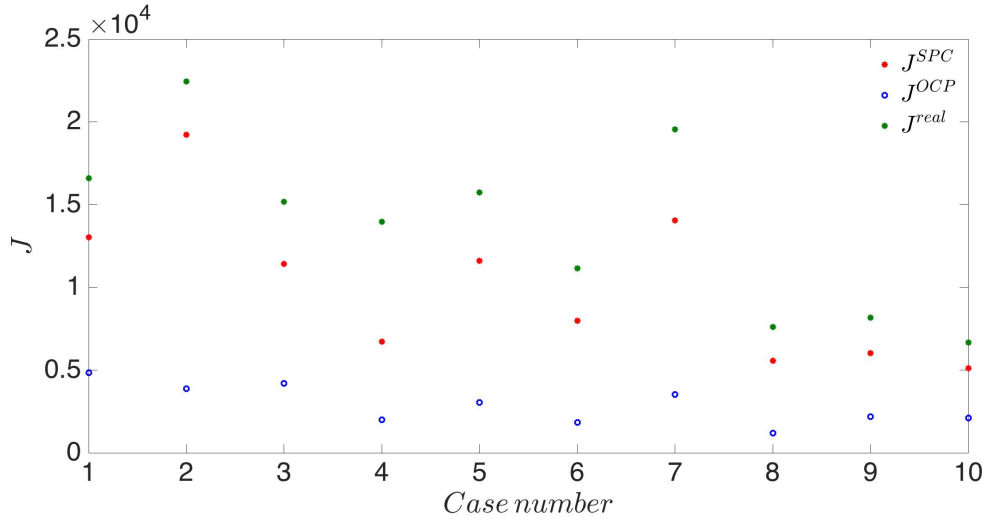


Figure 6.1: Cost value obtained for the control scheme when the controller is given by the positive control law, J^{PCL} , (red star), the cost value obtained for the control scheme when the controller is the solution of the optimal control problem J^{OCP} , (blue star) for the NMB level and the cost value obtained using the real signals J^{real} (green cross).

With this result we can conclude that both control strategies improve the trade-off between the amount of the drug administered and the reference tracking of the NMB level when compared with the real scenario. However, the controller obtained by solving the optimal control problem presents a lower cost. Thus we can conclude that its implementation has more benefits in terms of the amount of drug administered and the tracking of the reference NMB level.

6.2 Comparison of the BIS case results

Similarly to what was done in the previous section for the NMB level, here we compare the performance of the control strategies when applied to the control of the BIS level.

In this case, the functional cost is given by the equation:

$$J = \frac{1}{n} \sum_{t=0}^n \left(\left(y_{BIS}^{ref} - y_{BIS}(t) \right)^2 + \kappa \left(u^P(t) + u^R(t) \right)^2 \right), \quad (6.2)$$

Again, both strategies present a cost functional values lower than the values obtained using the real signals. Hence, we can conclude that both strategies improve the trade-off between the amount of drugs administered and the reference tracking of the BIS level when applied in the real context. Comparing the two control approaches, the controller obtained by solving the optimal control problem shows better results than the one obtained with the compartmental control law.

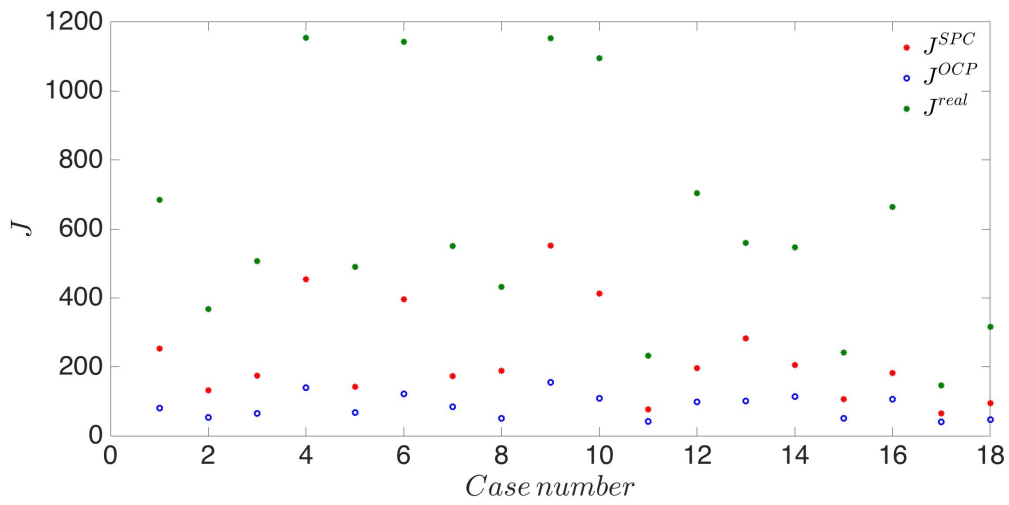


Figure 6.2: Cost value obtained for the control scheme when the controller is given by the positive control law, J^{PCL} , (red star), the cost value obtained for the control scheme when the controller is the solution of the optimal control problem J^{OCP} , (blue star) for the BIS level and the cost value obtained using the real signals J^{real} (green cross).

6.3 Clinical environment

The results obtained in this thesis support the incorporation of the state-feedback control approaches, with parameter identification, in clinical environment through the GALENO platform.

The GALENO platform was designed for automation in anesthesia during clinical practice and simulation environment (from 2010 to 2013). It consists of a Matlab package that allows the interface of control algorithms with medical equipment and is dedicated to the automatic control of the neuromuscular blockade and of the depth of anesthesia. The current version of this platform contains several control algorithms and system identification methods developed by the GALENO project researchers. Namely, a controller designed in a previous work based on the reduced model, Almeida et al. (2011), was included in this platform during the initial period of this thesis. This controller has been widely used in surgery rooms.

The extensive experience collected in clinical practice by using the aforementioned controller provided a particular sensitivity and knowledge about the complex process of automation in anesthesia. The methods and techniques developed for the control approaches proposed in this thesis were supported by this valuable and outstanding experience.

The implementation of the controller schemes proposed in this thesis both for neuromuscular blockade and depth of anesthesia is still under construction.

6.4 Main contributions and future work

The main contributions of this thesis were the design and its implementation, in a simulation environment, of two types of control laws for the reference tracking of the NMB and BIS levels during general anesthesia, namely: simplified positive mass control laws, and control laws designed based on suitable constrained optimal control problems that were solved using moment techniques.

As shown in Chapter 4, our simplified controller scheme has a similar performance as the previously proposed (non-simplified) control scheme using a positive mass control law based on the reduced parameter model. In turn a comparison of the non-simplified mass-controllers with and positive controllers based on PK/PD models has already been carried out in Almeida et al. (2011). This comparison led to the conclusion that the former controllers have similar performance as the latter, with the advantage of requiring the identification of fewer patient dependent parameters. Other control schemes, eg., based on PIDs, have been proposed in the literature Mendonça and Lago (1998), Lago et al. (1998). However their theoretical foundations, in particular in what concerns the proof of the convergence to the desired reference level, have not been established yet. Therefore here we have chosen only to compare the performance of the automatic controllers developed in this thesis with each other and with the manual control administrated by the anesthetist. It turns out that the controlled designed based on optimal control performs better than the simplified positive mass controller with respect to our cost function, while both of them perform better than manual control.

Despite the promising results of these two approaches, there was no opportunity of implementing them in clinical practice. In future work, the control schemes designed in this thesis should be implemented in the GALENO platform and validated in the operation room.

Appendix A

PK/PD parameters for the *atracurium* - NMB model

In Lago et al. (1998) a population model was proposed taking into account the works of Weatherley et al. (1983) and Ward et al. (1983). The corresponding simulation models were obtained assuming a multidimensional log-normal distribution for the pharmacokinetic and the pharmacodynamic parameters in equations (2.3) and (2.4). This appendix includes the values of the parameters k_{10} , k_{12} , k_{1e} , k_{e0} , k_{20} , k_{21} [min^{-1}] for 100 models.

Model	k_{10}	k_{12}	k_{1e}	k_{e0}	k_{20}	k_{21}	C_{50}	γ
1	0.1774	0.3125	0.0036	0.1014	0.0000	0.1184	0.6527	3.9896
2	0.1205	0.1794	0.0022	0.0900	0.0000	0.0902	0.6769	3.9476
3	0.0799	0.0733	0.0010	0.0902	0.0000	0.0766	0.6240	3.1482
4	0.1283	0.1674	0.0024	0.0970	0.0000	0.1345	0.6742	4.3279
5	0.0897	0.0982	0.0011	0.0949	0.0000	0.0858	0.6435	4.7597
6	0.1244	0.1548	0.0025	0.1020	0.0000	0.0960	0.6311	4.2727
7	0.1375	0.2139	0.0029	0.0971	0.0000	0.1115	0.6655	4.1166
8	0.1335	0.1657	0.0028	0.1029	0.0000	0.0900	0.6697	3.7007
9	0.1397	0.2234	0.0030	0.0998	0.0000	0.0876	0.6398	4.0910
10	0.1047	0.1928	0.0017	0.0836	0.0000	0.1556	0.6620	4.2006
11	0.1925	0.2737	0.0037	0.1018	0.0000	0.0969	0.6097	5.1818
12	0.0974	0.1364	0.0019	0.1062	0.0000	0.0962	0.6545	4.4898
13	0.1103	0.1123	0.0031	0.1177	0.0000	0.0770	0.6066	4.3392
14	0.1115	0.1166	0.0022	0.0963	0.0000	0.1013	0.6563	5.3965
15	0.0876	0.1092	0.0013	0.0879	0.0000	0.1283	0.6456	5.0480
16	0.0566	0.0513	0.0008	0.0980	0.0000	0.0934	0.6234	4.3575
17	0.1321	0.2148	0.0024	0.1022	0.0000	0.1170	0.6393	4.7257
18	0.1465	0.1881	0.0037	0.1075	0.0000	0.0887	0.6125	3.8534
19	0.1327	0.1811	0.0024	0.0946	0.0000	0.0919	0.7091	3.3303
20	0.1120	0.2281	0.0017	0.0928	0.0000	0.1193	0.6849	4.7091

Model	k_{10}	k_{12}	k_{1e}	k_{e0}	k_{20}	k_{21}	C_{50}	γ
21	0.1238	0.2225	0.0021	0.0907	0.0000	0.1290	0.6405	5.4086
22	0.0963	0.1213	0.0014	0.0923	0.0000	0.1160	0.6975	4.2585
23	0.1900	0.3681	0.0040	0.1107	0.0000	0.1156	0.6506	3.5436
24	0.0482	0.0171	0.0010	0.1116	0.0000	0.1468	0.6605	4.5706
25	0.1489	0.2881	0.0026	0.0892	0.0000	0.1400	0.6452	3.5223
26	0.1852	0.4011	0.0045	0.1003	0.0000	0.1433	0.6716	3.7446
27	0.1416	0.2297	0.0027	0.0904	0.0000	0.0986	0.6202	4.6149
28	0.1349	0.2371	0.0022	0.0936	0.0000	0.1273	0.6344	5.0500
29	0.0878	0.1541	0.0015	0.0986	0.0000	0.1402	0.6651	3.4746
30	0.1234	0.1584	0.0026	0.0996	0.0000	0.1421	0.6548	3.9473
31	0.1310	0.3080	0.0016	0.0850	0.0000	0.1545	0.6229	4.2800
32	0.1435	0.2061	0.0028	0.0928	0.0000	0.1246	0.6650	4.3926
33	0.1181	0.2236	0.0026	0.1056	0.0000	0.1550	0.6653	4.5267
34	0.0782	0.0766	0.0012	0.1055	0.0000	0.0783	0.6262	4.2578
35	0.1668	0.2349	0.0034	0.1016	0.0000	0.0947	0.6499	4.5096
36	0.1115	0.2591	0.0020	0.0938	0.0000	0.1338	0.6533	4.4695
37	0.0879	0.0852	0.0019	0.1042	0.0000	0.0944	0.6603	3.7671
38	0.1223	0.1194	0.0019	0.0853	0.0000	0.0779	0.6624	4.2315
39	0.1199	0.1484	0.0022	0.0953	0.0000	0.1079	0.6161	3.9712
40	0.1213	0.1323	0.0021	0.0973	0.0000	0.0939	0.6500	4.6327
41	0.1847	0.3332	0.0035	0.0928	0.0000	0.0921	0.6599	3.2811
42	0.0820	0.0595	0.0018	0.1077	0.0000	0.0962	0.6955	4.4275
43	0.1450	0.1850	0.0031	0.1039	0.0000	0.0919	0.6517	3.5224
44	0.0984	0.1937	0.0019	0.1032	0.0000	0.1195	0.6941	4.2905
45	0.1292	0.2144	0.0029	0.1019	0.0000	0.1303	0.6427	4.0431
46	0.0924	0.2195	0.0015	0.1028	0.0000	0.1627	0.6610	4.2986
47	0.0967	0.1366	0.0020	0.1068	0.0000	0.1223	0.6587	3.8199
48	0.1115	0.1398	0.0026	0.1028	0.0000	0.0901	0.6491	4.3942
49	0.0898	0.1442	0.0016	0.0951	0.0000	0.1378	0.6372	4.0812
50	0.1218	0.1962	0.0020	0.0857	0.0000	0.1268	0.6451	4.4704
51	0.1702	0.1668	0.0028	0.0905	0.0000	0.0640	0.6606	3.8730
52	0.0842	0.0866	0.0014	0.0997	0.0000	0.0918	0.6622	4.6127
53	0.1460	0.2514	0.0019	0.0900	0.0000	0.1112	0.6714	3.9129
54	0.1370	0.2256	0.0023	0.0888	0.0000	0.1185	0.6549	4.4047
55	0.1122	0.1623	0.0020	0.1012	0.0000	0.1341	0.6031	3.3747
56	0.1247	0.1974	0.0023	0.1093	0.0000	0.1332	0.6732	4.9630
57	0.1041	0.2139	0.0019	0.0928	0.0000	0.1616	0.6747	3.7667
58	0.1302	0.2279	0.0025	0.1038	0.0000	0.1329	0.6272	4.3128
59	0.1045	0.1505	0.0023	0.1132	0.0000	0.1117	0.6461	4.9081
60	0.1084	0.2048	0.0016	0.1033	0.0000	0.1457	0.6315	4.9170

Model	k_{10}	k_{12}	k_{1e}	k_{e0}	k_{20}	k_{21}	C_{50}	γ
61	0.1161	0.1674	0.0019	0.1010	0.0000	0.1137	0.6703	3.9240
62	0.1459	0.3182	0.0026	0.0993	0.0000	0.1360	0.6271	5.2428
63	0.0862	0.0753	0.0015	0.1012	0.0000	0.0826	0.5964	3.6932
64	0.1447	0.1877	0.0041	0.1284	0.0000	0.0853	0.6174	4.0606
65	0.1000	0.1246	0.0018	0.1025	0.0000	0.1078	0.6406	4.0815
66	0.1362	0.1847	0.0025	0.1067	0.0000	0.1033	0.6382	2.8659
67	0.1086	0.1302	0.0016	0.0957	0.0000	0.1075	0.6918	4.6857
68	0.1173	0.1698	0.0023	0.1007	0.0000	0.1013	0.6630	4.0857
69	0.0919	0.1365	0.0015	0.0962	0.0000	0.0983	0.6568	4.3558
70	0.1300	0.2155	0.0026	0.1029	0.0000	0.1237	0.6335	4.8719
71	0.0759	0.0649	0.0015	0.1009	0.0000	0.0902	0.6673	3.5112
72	0.2437	0.1614	0.0065	0.0975	0.0000	0.0481	0.6382	4.2303
73	0.1882	0.1927	0.0043	0.0985	0.0000	0.0771	0.6466	4.5427
74	0.1198	0.2061	0.0023	0.1009	0.0000	0.1148	0.6459	4.3404
75	0.1117	0.3284	0.0019	0.0904	0.0000	0.1672	0.6454	3.9773
76	0.0930	0.1434	0.0018	0.1090	0.0000	0.0993	0.5972	3.2956
77	0.1744	0.2811	0.0032	0.1065	0.0000	0.1070	0.6433	5.2459
78	0.0790	0.0562	0.0013	0.1117	0.0000	0.0756	0.6448	3.7874
79	0.1872	0.3480	0.0041	0.1075	0.0000	0.1037	0.6102	3.3890
80	0.0958	0.2025	0.0017	0.0955	0.0000	0.1326	0.6331	4.0243
81	0.1108	0.1855	0.0017	0.0930	0.0000	0.1108	0.6344	4.3891
82	0.1605	0.2562	0.0037	0.1005	0.0000	0.0983	0.6767	4.5957
83	0.0862	0.1163	0.0014	0.0929	0.0000	0.1312	0.6756	4.0209
84	0.1838	0.3813	0.0035	0.0948	0.0000	0.1085	0.6528	4.0483
85	0.0866	0.1152	0.0014	0.0901	0.0000	0.1313	0.5771	4.7046
86	0.1050	0.1912	0.0021	0.1020	0.0000	0.1193	0.6975	4.1069
87	0.1427	0.3536	0.0036	0.1003	0.0000	0.2232	0.6386	4.4922
88	0.0794	0.0712	0.0014	0.1019	0.0000	0.0876	0.6499	3.9735
89	0.1268	0.1750	0.0027	0.1059	0.0000	0.0859	0.6424	3.5674
90	0.2016	0.4729	0.0041	0.1001	0.0000	0.1328	0.6418	4.5014
91	0.1005	0.1230	0.0018	0.0994	0.0000	0.0991	0.6331	5.2730
92	0.1336	0.3644	0.0025	0.0892	0.0000	0.1777	0.6550	4.3442
93	0.1065	0.1434	0.0019	0.1020	0.0000	0.1284	0.6574	5.7029
94	0.2200	0.3158	0.0043	0.0932	0.0000	0.0978	0.6319	4.3254
95	0.1077	0.1059	0.0016	0.0911	0.0000	0.1013	0.6495	4.1183
96	0.1158	0.1709	0.0019	0.1014	0.0000	0.0935	0.6192	3.6866
97	0.1489	0.3262	0.0020	0.0920	0.0000	0.1588	0.6472	4.4492
98	0.1343	0.2337	0.0028	0.1064	0.0000	0.1296	0.6900	3.4982
99	0.1750	0.1562	0.0037	0.0911	0.0000	0.0742	0.6782	4.5144
100	0.1631	0.2333	0.0029	0.1000	0.0000	0.1081	0.6250	4.1006

Appendix B

Parameters values for the reduced NMB model

In Rocha et al. (2013) a population model was proposed for the reduced model for the NMB level, and 100 simulation models were obtained assuming a bivariate normal distribution for the parameters α and γ . These are listed in the following tables.

Model	α	γ
1	0.0448	2.2464
2	0.0412	2.9740
3	0.0378	1.8559
4	0.0395	2.0250
5	0.0335	4.5410
6	0.0487	1.8050
7	0.0377	2.8611
8	0.0495	1.3061
9	0.0389	2.2749
10	0.0428	1.8861
11	0.0298	2.8826
12	0.0335	3.9565
13	0.0454	3.1812
14	0.0338	4.1824
15	0.0409	2.6325
16	0.0353	3.2642
17	0.0366	1.9262
18	0.0303	2.6834
19	0.0306	4.6375
20	0.0436	3.1933

Model	α	γ
21	0.0371	3.0894
22	0.0330	1.9503
23	0.0332	3.2284
24	0.0428	2.7471
25	0.0370	2.3554
26	0.0405	2.7678
27	0.0398	5.8448
28	0.0421	2.1138
29	0.0398	1.5159
30	0.0303	1.3093
31	0.0396	2.0012
32	0.0445	1.8909
33	0.0419	1.6837
34	0.0258	6.7175
35	0.0358	3.7614
36	0.0355	3.4349
37	0.0393	2.9484
38	0.0345	1.1170
39	0.0374	4.5999
40	0.0480	2.2479

Model	α	γ
41	0.0427	1.8126
42	0.0390	1.3337
43	0.0323	3.0455
44	0.0370	5.2768
45	0.0382	2.9523
46	0.0343	3.7325
47	0.0355	2.6102
48	0.0399	3.5523
49	0.0477	1.3675
50	0.0255	4.7934
51	0.0315	3.5767
52	0.0445	2.2160
53	0.0409	2.6649
54	0.0358	4.5971
55	0.0399	2.5732
56	0.0321	3.9677
57	0.0319	1.9665
58	0.0393	3.7719
59	0.0474	4.0478
60	0.0420	2.0308

Model	α	γ
61	0.0345	2.0376
62	0.0429	1.7712
63	0.0359	3.4293
64	0.0334	2.2653
65	0.0349	2.7179
66	0.0340	1.8141
67	0.0362	3.8102
68	0.0408	1.9596
69	0.0316	3.9868
70	0.0395	3.2793
71	0.0446	2.2267
72	0.0383	2.8910
73	0.0417	2.2215
74	0.0371	2.3825
75	0.0512	3.0818
76	0.0432	2.4374
77	0.0281	2.2937
78	0.0376	4.4079
79	0.0282	2.3291
80	0.0439	2.7248

Model	α	γ
81	0.0397	1.9430
82	0.0413	2.2453
83	0.0428	2.7501
84	0.0491	3.0762
85	0.0355	2.4771
86	0.0366	3.0201
87	0.0411	2.3179
88	0.0435	2.4034
89	0.0314	2.0571
90	0.0343	2.7195
91	0.0376	4.2942
92	0.0254	2.6901
93	0.0448	1.5388
94	0.0318	4.9773
95	0.0447	3.4159
96	0.0330	3.7567
97	0.0413	1.5494
98	0.0425	4.0200
99	0.0364	2.2434
100	0.0408	1.6940

Appendix C

Real doses of *atracurium* and the corresponding NMB level

The following figures show the real NMB level obtained during ten general anesthetics and the administered *atracurium* dose given by the anesthesiologist.

1. Female patient with 82 year-old

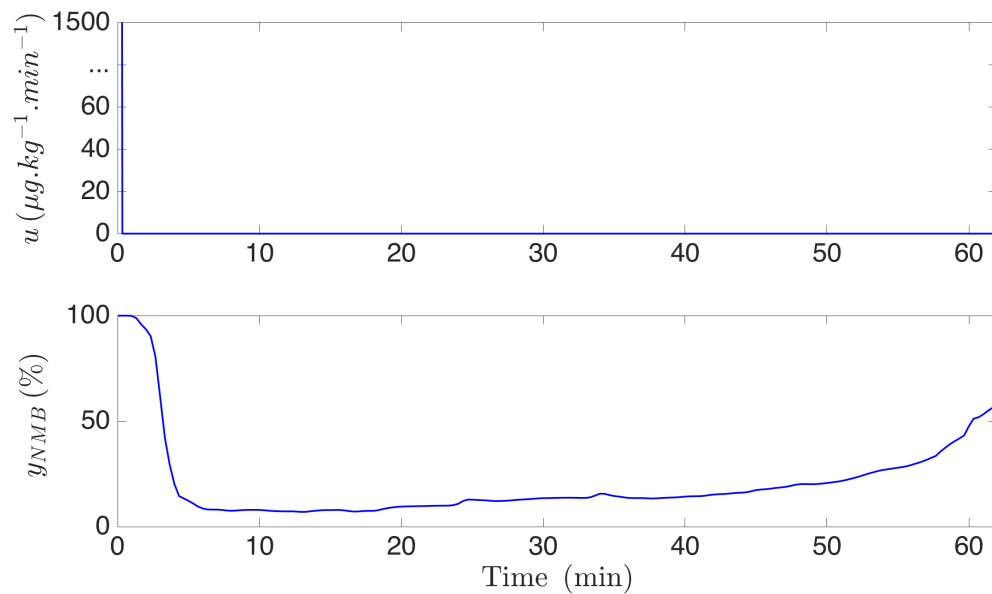


Figure C.1: NMB level and the *atracurium* dose profile of the patient number 1.

2. Female patient with 45 year-old

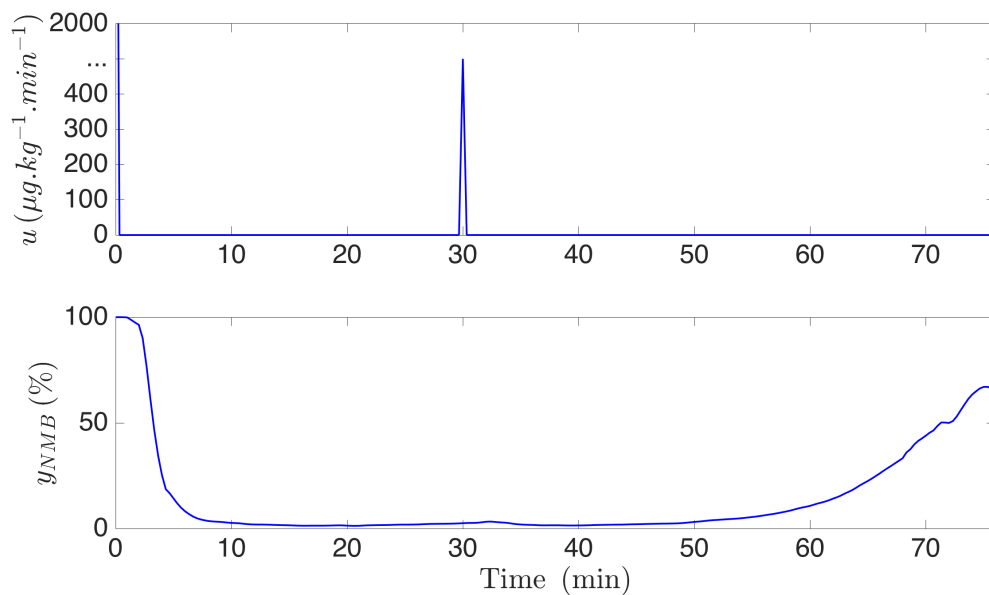


Figure C.2: NMB level and the *atracurium* dose profile of the patient number 2.

3. Female patient with 71 year-old

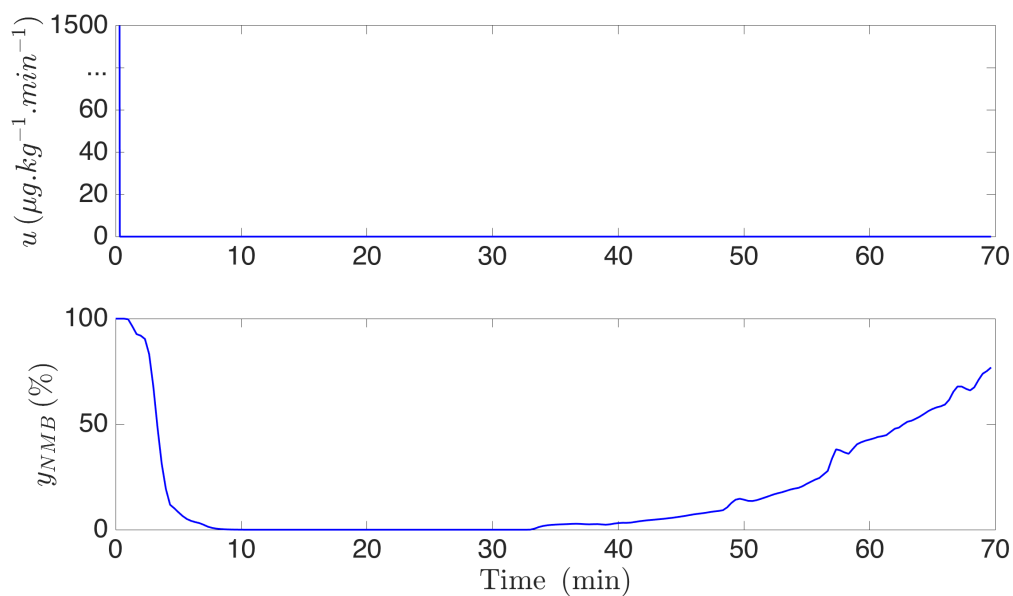


Figure C.3: NMB level and the *atracurium* dose profile of the patient number 3.

4. Female patient with 32 year-old

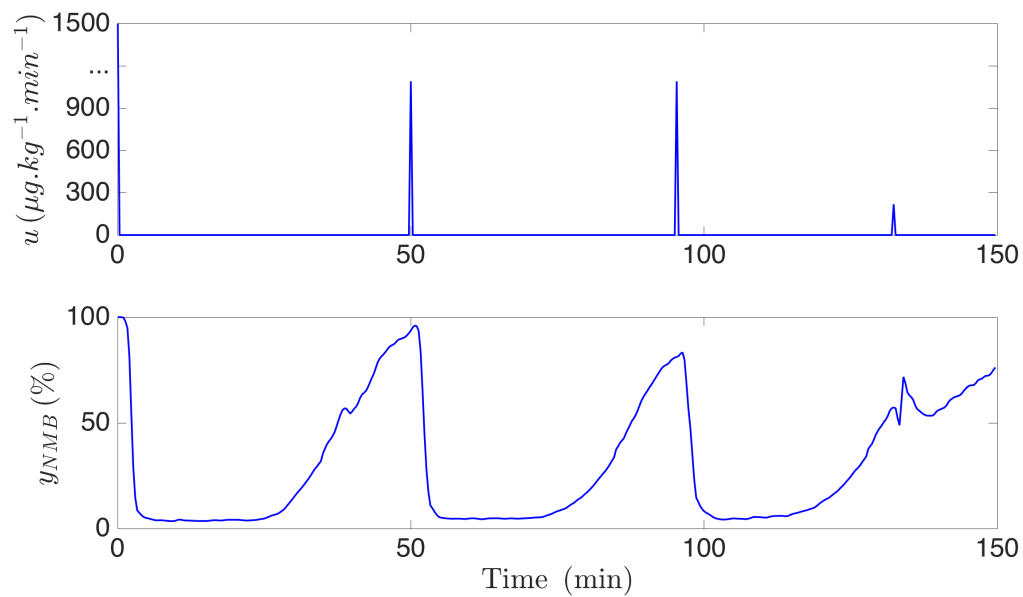


Figure C.4: NMB level and the *atracurium* dose profile of the patient number 4.

5. Female patient with 49 year-old

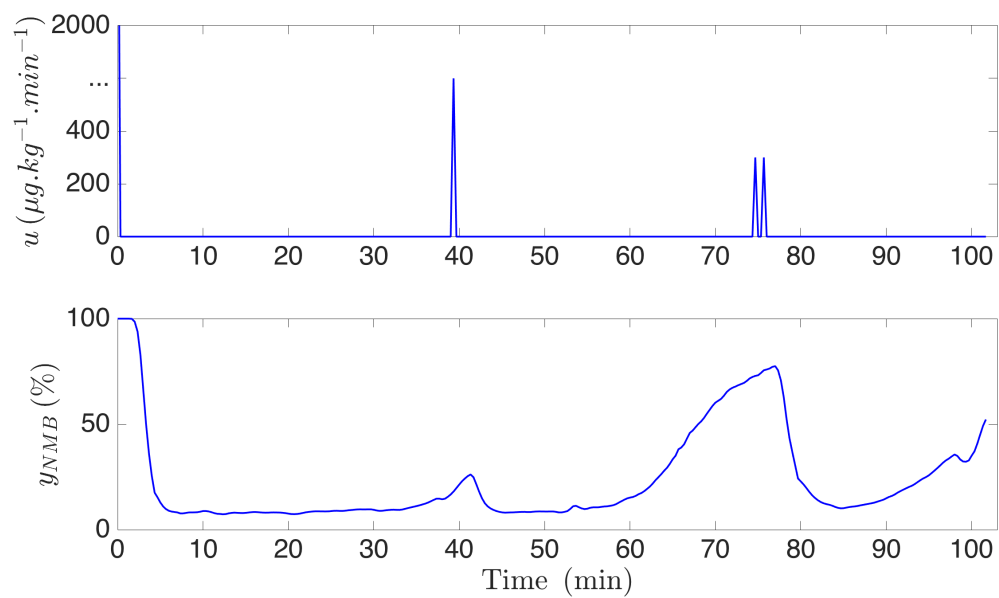


Figure C.5: NMB level and the *atracurium* dose profile of the patient number 5.

6. Female patient with 69 year-old

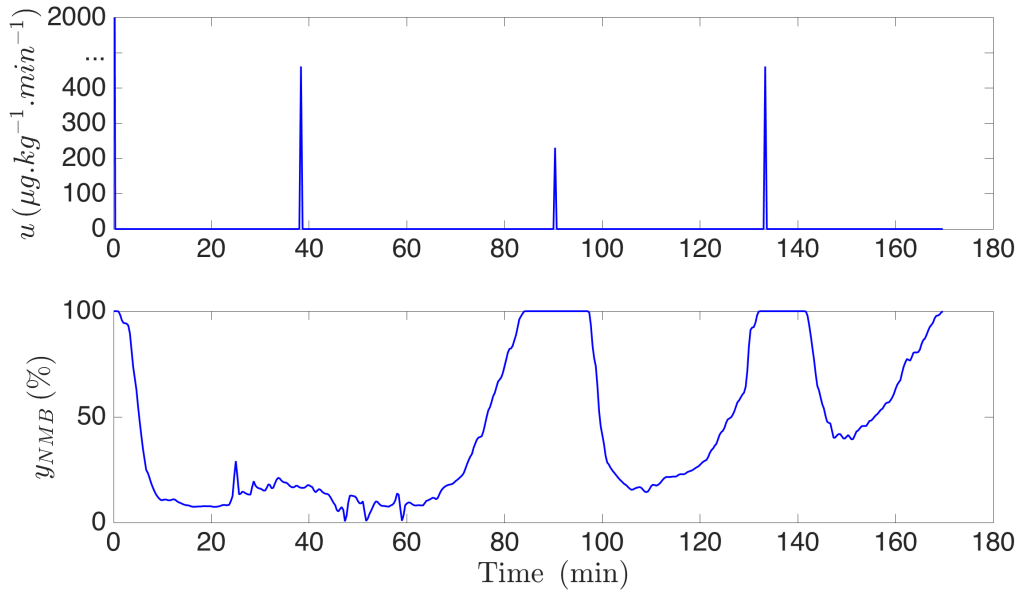


Figure C.6: NMB level and the *atracurium* dose profile of the patient number 6.

7. Male patient with 47 year-old

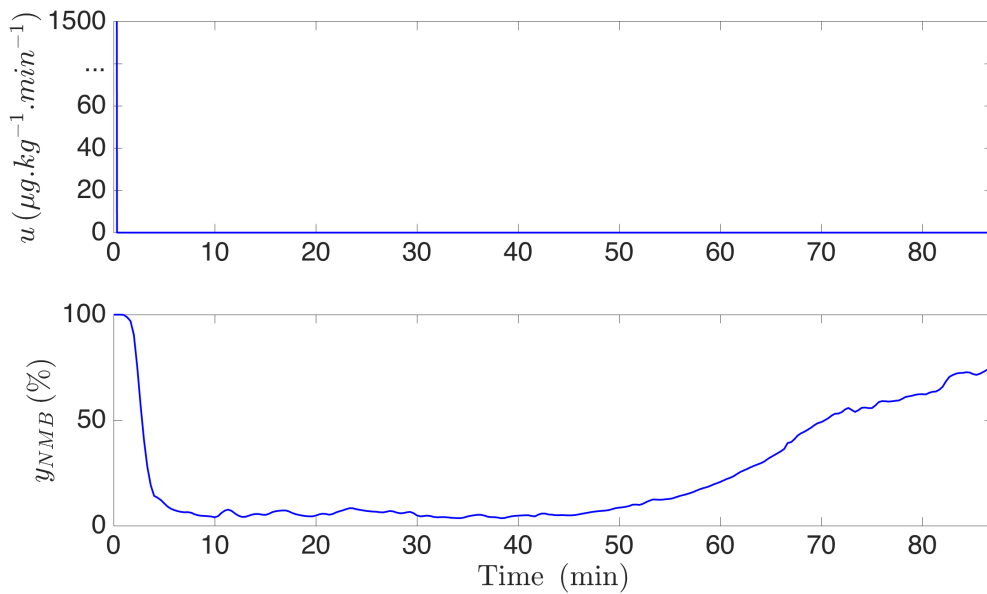
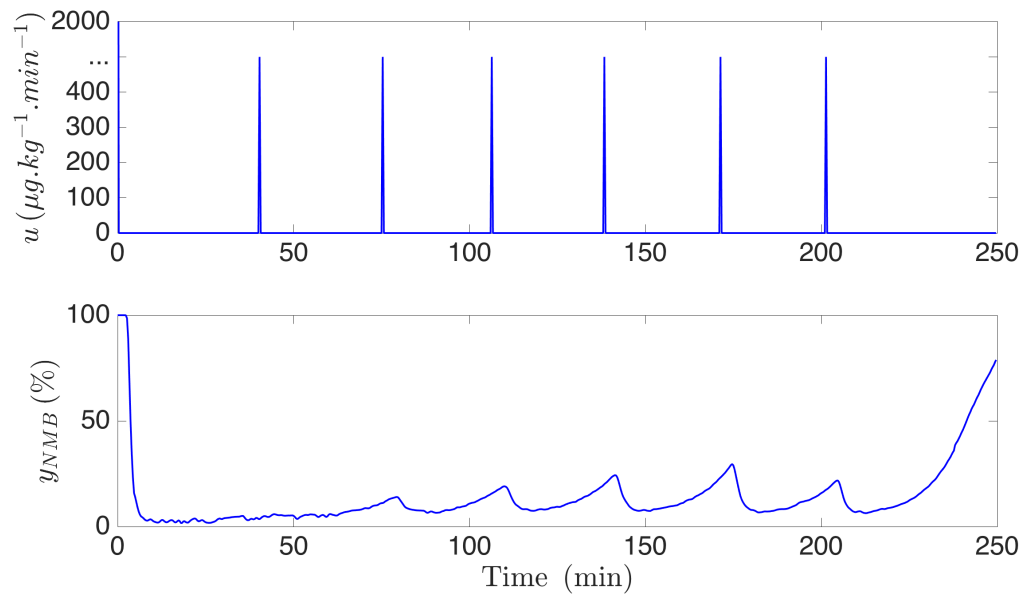
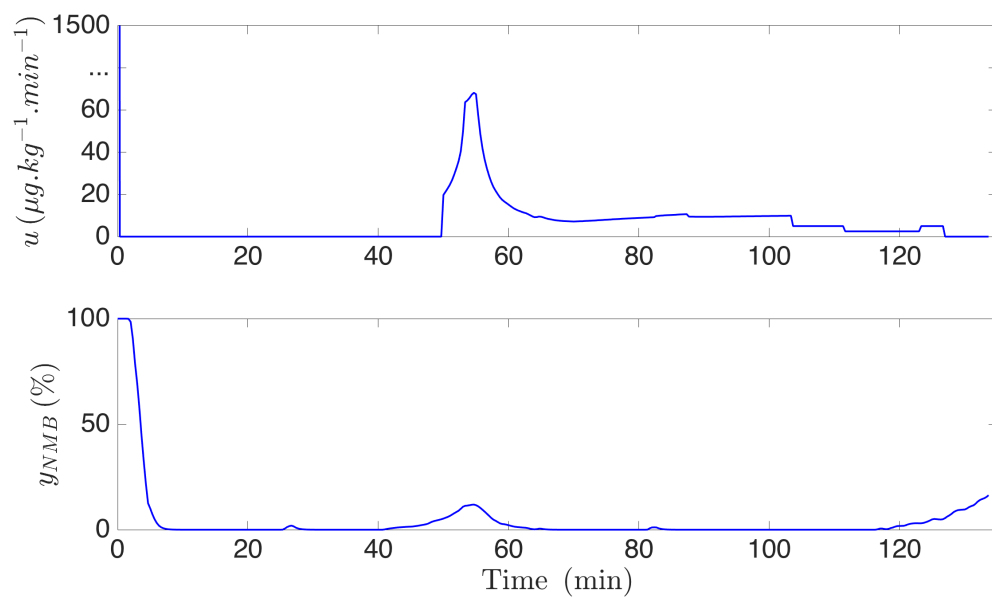


Figure C.7: NMB level and the *atracurium* dose profile of the patient number 7.

8. Male patient with 86 year-oldFigure C.8: NMB level and the *atracurium* dose profile of the patient number 8.**9. Male patient with 37 year-old**Figure C.9: NMB level and the *atracurium* dose profile of the patient number 9.

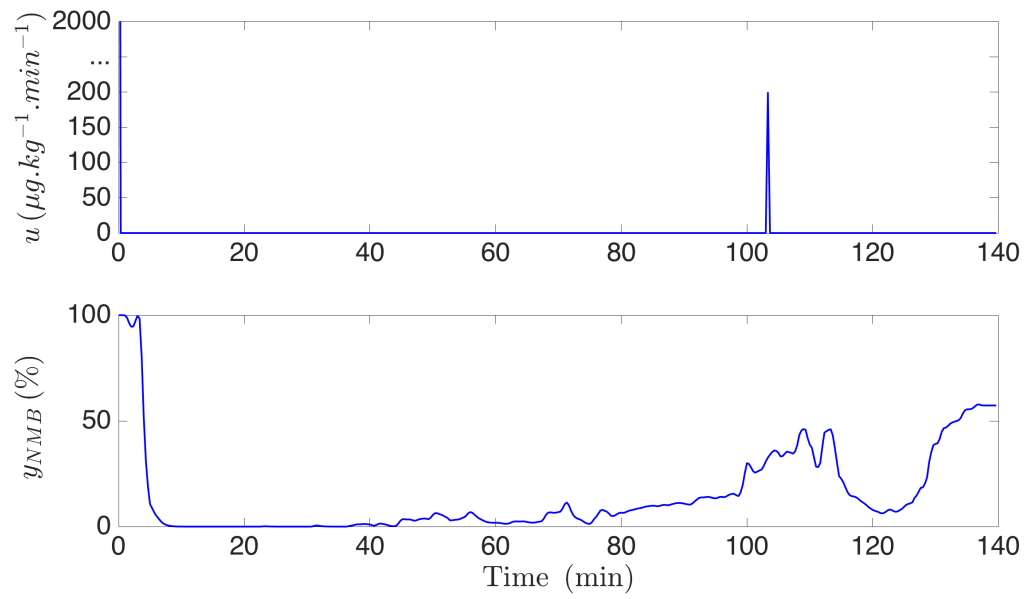
10. Male patient with 68 year-old

Figure C.10: NMB level and the *atracurium* dose profile of the patient number 10.

Appendix D

PK/PD parameter values for the BIS model

D.1 Schneider and Minto models

As mentioned, the PK/PD models used to simulate the BIS level take into account patient's information as the age, height, weight and gender. The models presented in the literature for *propofol* are Marsh's model, Marsh et al. (1991) and Schnider's model, Schnider et al. (1998), whereas for the opioid remifentanyl Minto's model, Minto et al. (1997), is adapted. Here, Schnider's model and Minto's model will be considered since that were the ones used in Chapter 2.

Note that, for both models the lean body mass (LBM) is computed as:

- Male: $1.10 \times \text{weight} - 128 \times \left(\frac{\text{weight}}{\text{height}}\right)^2$
- Female: $1.07 \times \text{weight} - 148 \times \left(\frac{\text{weight}}{\text{height}}\right)^2$

D.1.1 Schnider's model

The dynamic system that describes the exchange of the mass concentration between the compartments is represented by a state-space model with the following structure:

$$\begin{aligned} \dot{x}(t) &= \begin{bmatrix} -(k_{10} + k_{12} + k_{13}) & k_{21} \frac{V_2}{V_1} & k_{31} \frac{V_3}{V_1} & 0 \\ k_{12} \frac{V_1}{V_2} & -k_{21} & 0 & 0 \\ k_{13} \frac{V_1}{V_3} & 0 & -k_{30} & 0 \\ 0 & 0 & 0 & -k_{e0} \end{bmatrix} x(t) + \begin{bmatrix} \frac{1}{V_1} \\ 0 \\ 0 \\ 0 \end{bmatrix} u(t) \\ c_e(t) &= \begin{bmatrix} 0 & 0 & 0 & 1 \end{bmatrix} x(t) \end{aligned} \quad (\text{D.1})$$

The value of the parameters are obtained using the following equations, Schnider et al. (1998),

- $V_1 = 4.27$

- $V_2 = (18.9 - 0.391 \times (age - 53))$
- $V_3 = 238$
- $k_{10} = 0.443 + 0.0107 \times (weight - 77) - 0.0159 \times (LBM - 59) + 0.0062 \times (height - 177)$
- $k_{12} = 0.302 - 0.0056 \times (age - 53)$
- $k_{13} = 0.196$
- $k_{21} = \frac{1.29 - 0.024 \times (age - 53)}{18.9 - 0.391 \times (age - 53)}$
- $k_{31} = 0.0035$
- $k_{e0} = 0.456$

D.1.2 Minto's model

The dynamic model is equal to the one presented above (D.1) and the parameter values are obtained as, Minto et al. (1997),

- $V_1 = 5.1 - 0.0201 \times (age - 40) + 0.072 \times (LBM - 55)$
- $V_2 = 9.82 - 0.0811 \times (age - 40) + 0.108 \times (LBM - 55)$
- $V_3 = 5.42$
- $k_{10} = \frac{2.6 - 0.0162 \times (age - 40) + 0.0191 \times (LBM - 55)}{V_1}$
- $k_{12} = \frac{2.05 - 0.0301 \times (age - 40)}{V_1}$
- $k_{13} = \frac{0.076 - 0.00113 \times (age - 40)}{V_1}$
- $k_{21} = k_{12} \times \frac{V_1}{V_2}$
- $k_{31} = k_{13} \times \frac{V_1}{V_3}$
- $k_{e0} = 0.595 - 0.007 \times (age - 40)$

D.2 Database

The following table presents the data collected from 18 patients (gender, age, height, weight) as well as the corresponding parameters for the Hill equation. These latter were obtained using a hybrid method for parameter estimation presented in Mendonça et al. (2012).

Patient	Gender	Age	Height (cm)	Weight (kg)	C_{50}^P	C_{50}^R	β	γ
1	F	56	160	88	13.9395	41.6474	2.0321	3.3266
2	F	48	158	52	13.8766	40.2121	1.0133	3.3845
3	F	51	165	55	20.0000	28.2501	2.0196	2.3133
4	F	56	160	65	20.0000	52.2481	1.8930	3.2273
5	F	64	146	60	14.8483	99.9985	1.0702	2.9505
6	F	59	159	110	20.0000	89.0323	2.6169	3.3774
7	F	29	163	59	17.0831	61.0269	3.7297	3.1494
8	F	45	155	58	3.3464	100.0000	0.9172	0.0000
9	F	51	163	55	12.1717	31.1256	1.8645	2.8367
10	F	32	172	56	16.9091	13.7576	1.4517	2.7978
11	F	68	160	64	15.5170	100.0000	0.9334	3.4496
12	F	50	161	68	20.0000	100.0000	1.6649	3.2860
13	F	68	158	113	5.4124	34.6043	0.9882	2.8094
14	F	70	161	78	7.1976	36.6864	3.8213	2.2302
15	F	73	160	75	12.4128	16.3676	1.6771	2.4726
16	F	34	162	57	20.0000	46.0490	3.9302	2.9983
17	F	43	155	62	20.0000	49.7593	1.6096	3.2064
18	F	66	155	74	3.4326	99.9999	1.5613	3.2411

Appendix E

Parameters values for the reduced BIS model

The table presented here contains the parameter values for the reduced BIS model that were identified in Mendonça et al. (2012), for the 18 patients in the database presented in Appendix D, Section D.2.

Patient	ξ	η	m	ζ
1	0.0667	0.3989	2.1502	1.7695
2	0.0874	0.0670	4.7014	0.9365
3	0.0693	0.0482	1.1700	2.8186
4	0.0590	0.0425	1.4077	2.7594
5	0.0489	0.1269	1.4171	1.5627
6	0.0677	0.3373	1.1444	4.1247
7	0.0737	0.2793	0.8986	0.7812
8	0.0860	0.0212	1.4203	0.9780
9	0.0701	0.2837	1.2164	1.0956
10	0.1041	0.1038	1.9085	1.2165
11	0.0343	3.5768	2.5451	1.7097
12	0.0467	0.1254	1.4884	2.4877
13	0.0687	4.5413	2.3951	1.0859
14	0.0774	0.0397	1.5460	1.4038
15	0.0995	0.0377	2.0485	1.3706
16	0.0929	0.1205	1.5565	4.5194
17	0.0811	0.1033	2.0338	2.1978
18	0.1336	0.2307	1.2061	1.0846

References

- J. Almeida. Estratégia de controlo positivo para sistemas compartimentais do bloqueio neuromuscular. Master's thesis, Universidade do Porto, Faculdade de Ciências, 2010.
- J. Almeida, T. Mendonça, and P. Rocha. An improved strategy for neuromuscular blockade control with parameter uncertainty. In *Proc. 50th IEEE Conference on Decision and Control and European Control Conference*, pages 867 – 872, Orlando, FL, USA, 2011.
- J. Almeida, L.T. Paiva, T. Mendonça, and P. Rocha. Reference tracking of depth of anesthesia using optimal control. In *Proc. SIAM Conf. on Control and its Applications 2015*, pages 356 – 360, Paris, France, 2015a.
- J. Almeida, L.T. Paiva, T. Mendonça, and P. Rocha. An optimal control approach to reference level tracking in general anesthesia. In *Proc. 23rd Mediterranean Conference on Control and Automation*, pages 124 – 129, Torremolinos, Spain, 2015b.
- J. Almeida, T. Mendonça, and P. Rocha. A simplified control scheme for the depth of anesthesia. In *Proc. 4th IFAC Conference on Intelligent Control and Automation Sciences*, volume 49 (5), pages 230 – 235, Reims, France, 2016.
- J. Almeida, T. Mendonça, and P. Rocha. *A Simplified Control Approach for the Neuromuscular Blockade Level*, pages 37 – 44. Springer International Publishing, 2017.
- J. M. Bailey and W. M. Haddad. Drug dosing control in clinical pharmacology. *Control Systems Magazine, IEEE*, 25(2):35 – 51, 2005.
- G. Bastin and A. Provost. Feedback stabilization with positive control of dissipative compartmental systems. In *Proc. of the 15th International Symposium on Mathematical Theory of Networks and Systems*, 2010.
- C. Beauchier and J. J. Winkin. LQ-optimal control of positive linear systems. *Optimal Control Applications and Methods*, 31:547 – 566, 2010.
- R. Bellman. *Dynamic Programming*. Princeton University Press, Princeton, NJ, USA, 1957.
- Henri Bourlés. *Linear Systems*. John Wiley and Sons, Inc., 2013.
- B. H. Brown, R. Perks, M. Anthony, J. Asbury, and D. A. Linkens. Closed-loop control of muscle relaxation during surgery. *Clinical Physics and Physiological Measurement*, 1(3):203 – 210, 1980.
- R. S. Burachik, C. Y. Kaya, and S. N. Majeed. A duality approach for solving control-constrained linear-quadratic optimal control problems. *SIAM Journal Control Optimization*, 52:1423 – 1456, 2014.

- V. Chellaboina, W. M. Haddad, J. Ramakrishnan, and T. Hayakawa. Adaptive control for nonnegative dynamical systems with arbitrary time delay. In *Proc. 2006 American Control Conference*, pages 2676 – 2681, 2006.
- C. T. Chen. *Linear System Theory and Design*. Oxford University Press, Inc., 3rd edition, 1998.
- B. Costa, L. Paz, D. Caiado, S. Esteves, R. Rabiço, M. Seabra, Z. Moreira, J. Lemos, and T. Mendonça. Galeno: Computer aided system for modeling, monitoring and control in anesthesia (submitted). *IEEE Journal of Biomedical and Health Informatics*, -(–):–, 2014.
- P. L. Gambus and I.F. Trocóniz. Pharmacokinetic–pharmacodynamic modelling in anaesthesia. *British Journal Clinical Pharmacological*, 79(1):72–84, 2015.
- T. J. Gan, P. S. Glass, A. Windsor, F. Payne, C. Rosow, P. Sebel, and P. Manberg. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS Utility Study Group. *Anesthesiology*, 87(4):808 – 15, 1997.
- E. Gepts, F. Camu, I. Cockshott, and E.J. Douglas. Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesthesia and Analgesia*, 66:1256 – 1263, 1987.
- J. B. Glen. The development of ‘Diprifusor’: a TCI system for propofol. *Anaesthesia*, 53:13 – 21, 1998.
- K. Godfrey. *Compartmental models and their application*. Academic Press, 1983.
- R. Goebel and M. Subbotin. Continuous time linear quadratic regulator with control constraints via convex duality. *IEEE Transactions on Automatic Control*, 52:886–892, 2007.
- M. C. Grant and S. P. Boyd. The CVX Users’ Guide Release 2.1. Technical report, CVX Research, Inc., June 2015.
- B. Guignard. Monitoring analgesia. *Best practice & research. Clinical anaesthesiology*, 20(1): 161–180, 2006.
- T. M. Hemmerling. Neuromuscular Monitoring Part 1: A Review and Update. *Anesthesiology Rounds*, 3(3), 2004.
- C. M. Ionescu, R. Keyser, B. C. Torrico, T. Smet, M. M. Struys, and J. E. Normey-Rico. Robust predictive control strategy applied for propofol dosing using bis as a controlled variable during anesthesia. *IEEE Transactions on Biomedical Engineering*, 55(9):2161–2170, 2008.
- R. R. Jaklitsch and D. R. Westenskow. A model-based self-adjusting two-phase controller for vecuronium-induced muscle relaxation during anesthesia. *IEEE Transactions on Biomedical Engineering*, BME-34(8):583 – 594, 1987.
- E. W. Jensen, M. Jospin, P. L. Gambus, M. Vallverdu, and P. Caminal. Validation of the Index of Consciousness (IoC) during sedation/analgesia for ultrasonographic endoscopy. *Conf Proc IEEE Eng Med Biol Soc*, pages 5552 – 5555, 2008.
- R. E. Kalman. A New Approach to Linear Filtering and Prediction Problems. *Transactions of the ASME – Journal of Basic Engineering*, 82 (Series D):35–45, 1960.
- B. Kisanin and G.C. Agarwal. *Linear Control Systems - with solved problems and MATLAB examples*. University Series in Mathematics, 2001.

- H. Labbaf, M. Aliyari, and M. Teshnehlab. A new approach in drug delivery control in anesthesia. In *Proc. 2010 IEEE International Conference on Systems Man and Cybernetics*, pages 2064 – 2068, 2010.
- P. Lago, T. Mendonça, and L. Gonçalves. On-line autocalibration of a PID controller of neuromuscular blockade. In *Proc. IEEE International Conference on Control Applications*, pages 363 – 367, Trieste, Italy, 1998.
- P. Lago, T. Mendonça, and H. Azevedo. Comparison of on-line autocalibration techniques of a controller of neuromuscular blockade. In *Proc. 4th IFAC Symposium on Modelling and Control in Biomedical Systems*, pages 227 – 232, Germany, 2000.
- J. Lasserre. *Moments, Positive Polynomials and Their Applications*. Imperial College Press Optimization Series, 2009.
- J. B. Lasserre, D. Henrion, C. Prieur, and E. Trélat. Nonlinear optimal control via occupation measures and LMI relaxations. *SIAM Journal on Control and Optimization*, 47:1643 – 1666, 2008.
- N. Liu, T. Chazot, S. Hamada, A. Landais, N. Boichut, C. Dussaussoy, B. Trillat, L. Beydon, E. Samain, D. I. Sessler, and M. Fischler. Closed-loop co-administration of propofol and remifentanyl guided by bispectral index: A randomized multicenter study. *Anesthesia & Analgesia*, 112(3):546 — 557, 2011.
- J. Lofberg. Yalmip: A toolbox for modeling and optimization in matlab. In *Proc. IEEE International Symposium on Computer Aided Control Systems Design*, New Orleans, LA, USA, 2004.
- B. Marsh, M. White, N. Morton, and G. N. C. Kenny. Pharmacokinetic model driven infusion of propofol in children. *British Journal of Anaesthesia*, 67(1):41 – 48, 1991.
- C.D. McGrath and J.M. Hunter. Monitoring neuromuscular block. *Continuing Education in Anaesthesia, Critical Care & Pain*, 6(1):7 – 12, 2006.
- B. Meibohm and H. Derendorf. Basic concepts of pharmacokinetic/pharmacodynamic (pk/pd) modeling. *International Journal of Clinical Pharmacology and Therapeutics*, 34:401–413, 1997.
- T. Mendonça and P. Lago. PID control strategies for the automatic control of neuromuscular blockade. *Control Engineering Practice*, 6(10):1225 – 1231, 1998.
- T. Mendonça, P. Lago, H. Magalhães, A. Neves, and P. Rocha. On-line multiple model switching control implementation: A case study. In *Proc. 10th Mediterranean Conf. Control and Automation*, Lisbon, Portugal, 2002.
- T. Mendonça, C. Nunes, H. Magalhães, J. M. Lemos, and P. Amorim. Predictive adaptive control of unconsciousness - Exploiting remifentanyl as an accessible disturbance. In *Proc. IEEE International Conference on Control Applications*, pages 205 – 210, Munich, Germany, 2006.
- T. Mendonça, H. Alonso, M. M. Silva, S. Esteves, and M. Seabra. Comparing different identification approaches for the depth of anesthesia using bis measurements. *IFAC Proceedings Volumes*, 45(16):781 – 785, 2012.

- C. F. Minto, T. W. Schnider, T. D. Egan, E. Youngs, H. J. Lemmens, P. L. Gambus, V. Billard, J. F. Hoke, K. H. Moore, D. J. Hermann, K. T. Muir, J. W. Mandema, and S. L. Shafer. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanyl. I. Model development. *Anesthesiology*, 86:10 – 23, 1997.
- A. Neves, T. Mendonça, and P. Rocha. A Switching Control Strategy for Improving Drug Infusion. *International Journal of Control*, 82(12):2221 – 2234, 2009.
- F. Nogueira, T. Mendonça, and P. Rocha. Controlling the depth of anesthesia by a novel positive control strategy. *Computer Methods and Programs in Biomedicine*, 114:e87 – e97, 2014.
- L. T. Paiva. Optimal control for constrained hybrid system computational libraries and applications. Technical report, Faculdade de Engenharia, Universidade do Porto, 2013.
- G. Ritchie, J. P. Ebert, T. C. Jannett, I. Kissin, and L. C. Sheppard. A microcomputer based controller for neuromuscular block during surgery. *Annals of Biomedical Engineering*, 13(1): 3 – 15, 1985.
- C. Rocha, T. Mendonça, and M. E. Silva. Modelling neuromuscular blockade: a stochastic approach based on clinical data. *Mathematical and Computer Modelling of Dynamical Systems*, 19(6):540–556, 2013.
- I. M. Ross. *A Primer on Pontryagin’s Principle in Optimal Control*. Collegiate Publishers, 2009.
- B. Roszak and E. J. Davison. The servomechanism problem for unknown SISO positive systems via tuning regulators using clamping. In *Proc. 2008 IFAC World Congress*, pages 353 – 358. Seoul, Korea, 2008.
- T. W. Schnider, C. F. Minto, P. L. Gambus, C. Andresen, D. B. Goodale, S. L. Shafer, and E. J. Youngs. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology*, 8:1170 — 1182, 1998.
- M. Silva, T. Mendonça, I. Silva, and H. Magalhães. Statistical analysis of neuromuscular blockade response: contributions to an automatic controller calibration. *Computational Statistics & Data Analysis*, 49(3):955 – 968, 2005.
- M. M. Silva, C. Sousa, R. Sebastião, T. Mendonça, P. Rocha, and S. Esteves. Total mass tci driven by parametric estimation. In *Proc. 17th Mediterranean Conference on Control and Automation*, pages 1149 – 1154, 2009.
- M. M. Silva, T. Wigren, and T. Mendonça. Nonlinear identification of a minimal neuromuscular blockade model in anesthesia. *IEEE Transactions on Control Systems Technology*, 20(1):181 – 188, 2012.
- M.M. Silva, J.M. Lemos, A. Coito, B.A. Costa, T. Wigren, and T. Mendonça. Local identifiability and sensitivity analysis of neuromuscular blockade and depth of hypnosis models. *Computer Methods and Programs in Biomedicine*, 113(1):23 – 36, 2014a.
- M.M. Silva, T. Wigren, and T. Mendonça. A reduced MIMO Wiener model for recursive identification of the Depth of Anesthesia. *International Journal Adaptive Control and Signal Processing*, 28(12):1357 – 1371, 2014b.
- T. Söderström. *Discrete-Time Stochastic Systems: Estimation and Control*. Springer-Verlag New York, Inc., Secaucus, NJ, USA, 2nd edition, 2002.

- K. Soltesz, J. O. Hahn, G. A. Dumont, and J. M. Ansermino. Individualized PID control of depth of anesthesia based on patient model identification during the induction phase of anesthesia. In *Proc. 50th IEEE Conference on Decision and Control and European Control Conference*, pages 855 — 860, Orlando, Florida, 2011.
- J. F. Sturm. *Sedumi: a linear/ quadratic/ semidefinite solver for Matlab and Octave*. 2013. URL <http://github.com/sedumi/sedumi>.
- M. Teixeira, T. Mendonça, P. Rocha, and R. Rabiço. Automatic control of the NMB level in general anaesthesia with a switching total system mass control strategy. *Journal of Clinical Monitoring and Computing*, 28(6):501 – 512, 2014.
- H. Viertiö-Oja, V. Maja, M. Särkelä, P. Talja, N. Tenkanen, H. Tolvanen-Laakso, M. Paloheimo, A. Vakkuri, A. Yli-Hankala, and P. Meriläinen. Description of the entropy algorithm as applied in the Datex-Ohmeda S/5 Entropy Module. *Acta Anaesthesiologica Scandinavica*, 48(2):54 – 61, 2004.
- S. Ward, E. Neill, B. Weatherley, and I. Corall. Pharmacokinetics of atracurium besylate in healthy patients (after a single i.v. bolus dose). *British Journal of Anaesthesia*, 55:113 – 117, 1983.
- B. Weatherley, S. Williams, and E. Neill. Pharmacokinetics, pharmacodynamics and dose-response relationships of atracurium administered i.v. *British Journal of Anaesthesia*, 55:39s – 45s, 1983.
- G. Welch and G. Bishop. An introduction to the kalman filter. Technical report, Chapel Hill, NC, USA, 1995.
- T. Wigren. Recursive prediction error identification method using the nonlinear Wiener model. *Automatica*, 29(4):1011 – 1025, 1993.