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Nonlinear Modeling and Feedback Control of Drug Delivery in Anesthesia

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ACTA
UNIVERSITATIS
UPSALIENSIS
UPPSALA
2014

ISSN 1651-6214
ISBN 978-91-554-9054-6
urn:nbn:se:uu:diva-233290

Dissertation presented at Uppsala University to be publicly examined in ITC 2347, Lägerhyddsvägen 2, Uppsala, Friday, 21 November 2014 at 09:15 for the degree of Doctor of Philosophy. The examination will be conducted in English. Faculty examiner: Prof. Robain De Keyser (Ghent University, Belgium).

Abstract

Silva, M. M. 2014. Nonlinear Modeling and Feedback Control of Drug Delivery in Anesthesia. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Science and Technology* 1187. 75 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-554-9054-6.

General anesthesia is a drug-induced reversible state where neuromuscular blockade (NMB), hypnosis, and analgesia (jointly denoted by depth of anesthesia - DoA) are guaranteed. This thesis concerns mathematical modeling and feedback control of the effect of the muscle relaxants atracurium and rocuronium, the hypnotic propofol, and the analgesic remifentanil. It is motivated by the need to reduce incidences of awareness and overdose-related post-operative complications that occur in standard clinical practice. A major challenge for identification in closed-loop is the poor excitation provided by the feedback signal. This applies to the case of drugs administered in closed-loop. As a result, the standard models for the effect of anesthetics appear to be over-parameterized. This deteriorates the result of system identification and prevents individualized control.

In the first part of the thesis, minimally parameterized models for the single-input single-output NMB and the multiple-input single-output DoA are developed, using real data. The models have a nonlinear Wiener structure: linear time-invariant dynamics cascaded with a static nonlinearity. The proposed models are shown to improve identifiability as compared to the standard ones.

The second part of the thesis presents system identification methods for Wiener systems: a batch prediction error method, and two recursive techniques, one based on the extended Kalman filter, and another based on the particle filter. Algorithms are given for both the NMB and the DoA using the minimally parameterized models.

Nonlinear adaptive controllers are proposed in the third part of the thesis. Using the model parameter estimates from the extended Kalman filter, the controller performs an online inversion of the Wiener nonlinearity. A pole-placement controller or a linear quadratic Gaussian controller is used for the linearized system. Results show good reference tracking performance both in simulation and in real trials.

Relating to patient safety, the existence of undesirable sustained oscillations as consequence of Andronov-Hopf bifurcations for a NMB PID-controlled system is analyzed. Essentially the same bifurcations are observed in the standard and the minimally parameterized models, confirming the ability of the latter to predict the nonlinear behavior of the closed-loop system. Methods to design oscillation-free controllers are outlined.

Keywords: anesthesia, drug delivery, feedback control, nonlinear modeling, pharmacokinetics/pharmacodynamics, PID control, system identification, Wiener model

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ISSN 1651-6214
ISBN 978-91-554-9054-6
urn:nbn:se:uu:diva-233290 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-233290)

Para os meus pais

List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I 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, Jan. 2012.

II M.M. Silva, T. Mendonça, and T. Wigren. Online nonlinear identification of the effect of drugs in anaesthesia using a minimal parameterization and BIS measurements. In *Proc. American Control Conference (ACC)*, Baltimore, MD, USA, pages 4379-4384, June 30 - July 2, 2010.

III O. Rosén, M.M. Silva, and A. Medvedev. Nonlinear estimation of a parsimonious Wiener model for the neuromuscular blockade in closed-loop anesthesia. In *Proc. 19th World Congress of the International Federation of Automatic Control*, Cape Town, South Africa, pages 9258-9264, Aug. 24-29, 2014.

IV 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, Jan. 2014.

V M.M. Silva, T. Mendonça, and T. Wigren. Nonlinear adaptive control of the neuromuscular blockade in anesthesia. In *Proc. 50th IEEE Conference on Decision and Control and European Control Conference (CDC-ECC)*, Orlando, FL, USA, pages 41-46, Dec. 12-15, 2011.

VI M.M. Silva, T. Wigren, and T. Mendonça. Exactly linearizing adaptive control of propofol and remifentanil using a reduced Wiener model for the depth of anesthesia. In *Proc. 51st IEEE Conference on Decision and Control (CDC)*, Maui, HI, USA, pages 368-373, Dec. 10-13, 2012.

VII M.M. Silva, L. Paz, T. Wigren, and T. Mendonça. Performance of an adaptive controller for the neuromuscular blockade based on inversion of a Wiener model. *Asian Journal of Control*, Sept. 2013. (early view available at http://onlinelibrary.wiley.com/doi/10.1002/asjc.981/abstract)

VIII Z.T. Zhusubaliyev, A. Medvedev, and M.M. Silva. Bifurcation analysis of PID controlled neuromuscular blockade in closed-loop anesthesia. *Journal of Process Control*, Sept. 2013. (submitted)

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Contents

Acronyms

AEP	auditory evoked potentials
aGPC	adaptive generalized predictive control
AMG	acceleromyography
ARMAX	autoregressive moving average with exogenous signal
ARX	autoregressive with exogenous signal
BIS	bispectral index
DoA	depth of anesthesia
ECG	electrocardiogram
EEG	electroencephalogram
EKF	extended Kalman filter
EMG	electromyography
EPSAC	extended prediction self-adaptive control
FIR	finite impulse response
FOPTD	first-order plus time-delay
GDAD	Galeno-data acquisition drivers
GMCA	Galeno-monitoring and control of anesthesia
GPC	generalized predictive control
ICU	intensive care unit
IMC	internal model control
LPV	linear parameter-varying
LTI	linear time-invariant
MISO	multiple-input single-output
MPC	model predictive control
MPP	minimally parameterized parsimonious
MRAS	model reference adaptive system
NARMAX	nonlinear autoregressive moving average with exogenous signal
NARX	nonlinear autoregressive with exogenous signal
NFIR	nonlinear finite impulse response
NMB	neuromuscular blockade
NMPC	nonlinear model predictive control

PD	pharmacodynamic
pdf	probability density function
pe	persistently exciting
PEM	prediction error method
PF	particle filter
PID	proportional-integral-derivative
PK	pharmacokinetic
RPEM	recursive prediction error method
SISO	single-input single-output
SMC	sequential Monte Carlo
STR	self-tuning regulator
TCI	target-controlled infusion
TIVA	total intravenous anesthesia
TOF	train-of-four
WMPC	Wiener model predictive control

1. Introduction

Ranging from automotive industry to telecommunications and systems biology, the impact of control technology in the modern society is undeniable. In fact, the introduction of control theory in engineered systems decreased the variation in manufactured products and processes, which in turn resulted in an increase in performance, reduction of costs and enhanced safety [118]. This overall improvement due to automation drives the efforts to decrease the variation in medical protocols, which is likewise critical to the concept of medical quality [84, 112]. However, despite the great achievements in the medical field, with e.g. the introduction of the pacemaker or the development of an artificial pancreas [38], the potential of closed-loop controllers in the daily clinical practice is still poorly exploited. In anesthesia, several attempts have been made to completely automatize the drug delivery to patients but no technique has become widely used in the daily clinical practice. The mismatch between research and practice is mainly due to legal regulations. In fact, the likelihood of approval of any closed-loop control strategy by the regulatory entities is likely to increase with demonstration of a clinically significant safety benefit [86]. Those benefits may encompass a reduction of the incidence of underdose-related awareness (i.e. anesthesia too light), or of overdose-related (i.e. anesthesia too deep) post-operative complications as compared to standard clinical practice. Oscillations in the measured variables are typical nonlinear behaviors that can lead to under- and overdosing of anesthetics, and should therefore be avoided. Examples of cases where oscillations were observed in clinical trials of closed-loop systems include [7, 54, 64, 91].

From the engineering point of view, two crucial aspects that hamper the flourishing of closed-loop control strategies for drug delivery are the lack of reliable sensors to represent the state of the system, and the lack of suitable models to describe the processes to be controlled [112]. In fact, if the purpose of the modeling is to obtain deep insight on the physiology behind the process, first principles models based on the laws of physics are usually preferred. On the contrary, in case the purpose is either prediction of the behavior of the system or model-based control, low-complexity models derived from e.g. system identification experiments are most often preferred [148]. This choice is specially important in environments that are not data-rich, or where the inputs are not allowed to be arbitrarily selected for best identification purposes, which is precisely the case of general anesthesia.

1.1 Contributions

The first contribution of this thesis is the development of new models for the effect of drugs in anesthesia. The proposed models have few parameters to cope with the poor excitatory properties of the input signals commonly used in the clinical practice. A two-parameters single-input single-output (SISO) model for the atracurium- or rocuronium-induced neuromuscular blockade (NMB) is proposed in Paper I, and a four-parameters multiple-input single-output (MISO) model for the propofol/remifentanil depth of anesthesia (DoA) is proposed in Paper II. These minimally parameterized parsimonious (MPP) models have a nonlinear Wiener structure and were developed using real data.

The second contribution is the development of nonlinear batch (prediction error method - PEM) and recursive (extended Kalman filter - EKF) system identification methodologies for both the NMB and the DoA MPP models, in Papers I and II, respectively. Paper III addresses the recursive identification of the MPP model for the NMB. The performance of two popular nonlinear estimation techniques, namely the EKF and the particle filter (PF), is evaluated on synthetic and real data.

The third contribution is the sensitivity and local identifiability analysis of both the standard pharmacokinetic/pharmacodynamic (PK/PD) models and the MPP models, in Paper IV. The results show that the proposed models with few parameters have better identifiability properties than the standard models, which supports the idea of using MPP models for individualization and control purposes.

The fourth contribution is the development of nonlinear adaptive controllers based on the inversion of the nonlinearity of the Wiener models. The structure uses the model parameters recursively estimated by the EKF. Papers V and VII present both simulation and clinical closed-loop control results for the case of the NMB, respectively. Paper VI concerns the control of the DoA in simulation.

The fifth contribution, in Paper VIII, is a mathematical assessment of the existence of nonlinear sustained oscillations in the proportional-integral-derivative (PID)-controlled system for the atracurium-induced NMB as a consequence of Andronov-Hopf bifurcations. The analysis is performed for both the standard PK/PD and the MPP models and it points towards patient safety in automatically controlled drug delivery in anesthesia. Methods to design oscillation-free controllers are outlined.

1.2 Outline

In the end of this chapter papers by the author dealing with the same subject but not included in the thesis are listed. The remainder of the introduction to the thesis is organized in three chapters as follows.

Chapter 2 gives an overview of general anesthesia.

Section 2.1 describes the main components of general anesthesia, and their corresponding drugs and monitoring devices. Section 2.2 summarizes the different temporal phases in a general anesthesia. Section 2.3 presents the three administration regimens that are used by the anesthesiologists and provides the main challenges for the successful development of closed-loop controllers in anesthesia.

Chapter 3 concerns mathematical modeling.

Section 3.1 presents some basic structures of nonlinear models and identification methods. Section 3.2 gives an overview of identifiability in the system identification framework. Section 3.3 covers the input requirements for linear models and nonlinear Wiener models. Section 3.4 describes the different models available in the literature for the effect of the muscle relaxants atracurium and rocuronium, the hypnotic propofol and the analgesic remifentanil.

Chapter 4 presents a background on control, specially focusing on nonlinear feedback control.

Section 4.1 presents the main goals for the design of automatic controllers for drug delivery in anesthesia. Section 4.2 discusses general feedback control schemes and their use in control of anesthesia is reviewed. Section 4.3 covers the case of nonlinear feedback control of Wiener systems. Section 4.4 describes the Galeno platform that was used for the collection of real data and clinical trials for the work in this thesis. Section 4.5 covers the topic of patient safety, and introduces the issue of bifurcation and sustained oscillations in closed-loop anesthesia.

List of papers not included in the thesis

The following papers are not included in the thesis but are related to it and relevant for its contents.

Journal Papers

- M.M. Silva, T. Wigren, and T. Mendonça. A reduced MIMO Wiener model for recursive identification of the depth of anesthesia. *International Journal of Adaptive Control and Signal Processing*, Oct. 2013. (early view available at http://onlinelibrary.wiley.com/doi/10.1002/acs.2447/abstract)

- R. Sebastião, M.M. Silva, R. Rabiço, J. Gama, and T. Mendonça. Real-time algorithm for changes detection in depth of anesthesia signals. *Evolving Systems*, Springer Berlin / Heidelberg, 4(1): 3-12, 2013.

Conference Papers

- L.A. Paz, M.M. Silva, S. Esteves, R. Rabiço, and T. Mendonça. Automated total intravenous anesthesia (amTIVA) from induction to recovery. In *Proc. 9th IEEE International Symposium on Medical Measurement and Applications (MeMeA)*, Lisbon, Portugal, pages 102-107, June 11-12, 2014.
- Z.T. Zhusubaliyev, A. Medvedev, and M.M. Silva. Nonlinear dynamics in closed-loop anesthesia: pharmacokinetic/ pharmacodynamic model under PID-feedback. In *Proc. American Control Conference (ACC)*, Portland, OR, USA, pages 5496-5501, June 4-6, 2014.
- Z.T. Zhusubaliyev, A. Medvedev, and M.M. Silva. Bifurcation analysis for PID-controller tuning based on a minimal neuromuscular blockade model in closed-loop anesthesia. In *Proc. 52nd IEEE Conference on Decision and Control (CDC)*, Florence, Italy, pages 213-218, Dec. 10-13, 2013.
- D.V. Caiado, J.M. Lemos, B.A. Costa, M.M. Silva, and T.Mendonça. Design of depth of anesthesia controllers in the presence of model uncertainty. In *Proc. 21st Mediterranean Conference on Control and Automation (MED)*, Crete, Greece, pages 213-218, June 25-28, 2013. (invited session paper)
- L.A. Paz, M.M. Silva, S. Esteves, and T. Mendonça. Self-calibrating total-mass controller for the neuromuscular blockade matching the anesthesiologists' mindset. In *Proc. 21st Mediterranean Conference on Control and Automation (MED)*, Crete, Greece, pages 723-728, June 25-28, 2013.
- M.M. Silva, T. Wigren, A. Medvedev, and T. Mendonça. Quantification of the multiplicative uncertainty in the linearized minimally parameterized parsimonious Wiener model for the neuromuscular blockade in closed-loop anesthesia. In *Proc. 21st Mediterranean Conference on Control and Automation (MED)*, Crete, Greece, pages 703-708, June 25-28, 2013.
- R. Sebastião, M.M. Silva, R. Rabiço, J. Gama, and T. Mendonça. Online evaluation of a changes detection algorithm for depth of anesthesia signals. In *Proc. 8th Symposium on Biological and Medical Systems of the International Federation of Automatic Control (BMS)*, Budapest, Hungary, A-0076, Aug. 29-31, 2012. (invited session paper)

- M.M. Silva, R. Rabiço, T. Mendonça, and T. Wigren. Control of rocuronium-induced neuromuscular blockade via online identification of a two-parameters Wiener model. In *Proc. 16th Symposium on System Identification of the International Federation of Automatic Control (SYSID)*, Brussels, Belgium, pages 571-576, July 11-13, 2012. (invited session paper)
- T. Mendonça, H. Alonso, M.M. Silva, S. Esteves, and M. Seabra. Comparing different identification approaches for the depth of anesthesia using BIS measurements. In *Proc. 16th Symposium on System Identification of the International Federation of Automatic Control (SYSID)*, Brussels, Belgium, pages 781-785, July 11-13, 2012. (invited session paper)
- R. Sebastião, M.M. Silva, J. Gama, and T. Mendonça. Contributions to a decision support system based on depth of anesthesia signals. In *Proc. 25th IEEE International Symposium on Computer-Based Medical Systems (CBMS)*, Rome, Italy, June 20-22, 2012.
- M.M. Silva, and T. Wigren. Adaptive control of propofol-induced hypnosis in anesthesia using a minimally parameterized Wiener model. In *Proc. Reglermöte*, Uppsala, Sweden, June 13-14, 2012.
- M.M. Silva. Prediction error identification of minimally parameterized Wiener models in anesthesia. In *Proc. 18th World Congress of the International Federation of Automatic Control*, Milan, Italy, pages 5615-5620, Aug. 28 - Sept. 2, 2011.
- J. Almeida, M.M. Silva, T. Mendonça, and P. Rocha. A compartmental model-based control strategy for neuromuscular blockade level. In *Proc. 18th World Congress of the International Federation of Automatic Control*, Milan, Italy, pages 599-604, Aug. 28 - Sep. 2, 2011.
- M.M. Silva, J. Almeida, T. Wigren, and T. Mendonça. Merging PK/PD information in a minimally parameterized model of the neuromuscular blockade. In *Proc. 32nd International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, Buenos Aires, Argentina, pages 4602-4605, Aug. 31 - Sept. 4, 2010.
- J. Almeida, M.M. Silva, T. Wigren, and T. Mendonça. Contributions to the initialization of online identification algorithms for anaesthesia: the neuromuscular blockade case study. In *Proc. 18th Mediterranean Conference on Automation and Control (MED)*, Marrakech, Morocco, pages 1341-1346, June 23-25, 2010.

Technical Reports

- M.M. Silva, T. Wigren, and T. Mendonça. An adaptive controller for propofol in anesthesia under synergistic remifentanil distur-

bances. *Technical Report 2012-011*, Department of Information Technology, Uppsala University, May 2012.

- M.M. Silva, T. Mendonça, and T. Wigren. Online nonlinear identification of the effect of drugs in anaesthesia using a minimal parameterization and BIS measurements. *Technical Report 2010-008*, Department of Information Technology, Uppsala University, Mar. 2010.
- M.M. Silva, T. Wigren, and T. Mendonça. Nonlinear identification of a minimal neuromuscular blockade model in anaesthesia. *Technical Report 2009-023*, Department of Information Technology, Uppsala University, Sept. 2009.

2. General anesthesia

General anesthesia is a drug-induced, reversible condition that includes specific behavioral and physiological traits, namely akinesia, unconsciousness, amnesia, and analgesia, with concomitant stability of the autonomic, cardiovascular, respiratory, and thermoregulatory systems [25].

2.1 Components, corresponding drugs and monitoring

The four traits mentioned above are traditionally divided into three categories: neuromuscular blockade (NMB) related to akinesia, hypnosis relating to unconsciousness and amnesia, and analgesia.

2.1.1 Neuromuscular blockade

The NMB is related to akinesia, i.e. lack of movement. Muscle relaxants are the drugs that mostly induce NMB by blocking the acetylcholine-mediated neuromuscular transmission at the neuromuscular junction and can be of two major types: polarizing and non-depolarizing ones.

Succinylcholine is one example of a polarizing muscle relaxant. Similarly to acetylcholine, it induces NMB by binding itself to post-synaptic nicotinic acetylcholine receptors, depolarizing the plasma membrane of the muscle fiber. When voltage-sensitive sodium channels sense this membrane depolarization, they first open and then close and become inactivated. The membrane potential must be reset before the sodium channels can be re-activated. This is a very rapid process with acetylcholine, as it is hydrolysed by acetylcholinesterase within the synaptic cleft. However, succinylcholine is not metabolized by acetylcholinesterase. Hence, a prolonged activation of the succinylcholine receptors is produced. The sodium receptors at the end-plate and the peri-junctional zone remain inactivated and junctional transmission is blocked. The muscle becomes flaccid [11].

The majority of the clinically relevant muscle relaxants nowadays is however the non-depolarizing ones. They act as competitive antagonists against acetylcholine at the site of post-synaptic nicotinic acetylcholine receptors, binding to the receptors but not activating them, hence not depolarizing the muscle fibers. With antagonist block, there is a gradual

reduction in end-plate potential until it fails to reach the threshold to fire off a propagating action potential to produce muscle contraction [11]. Atracurium and rocuronium are the two non-depolarizing muscle relaxants used in the work presented in this thesis.

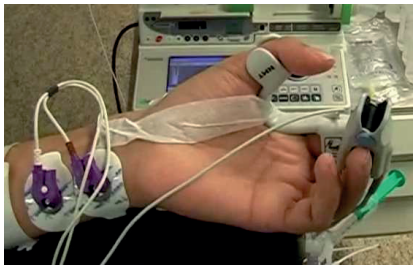
The need for muscle relaxant administration and NMB monitoring in general anesthesia is three-fold. First, during induction, complete muscle relaxation has been shown to improve the intubation conditions with reduction of post-operative side-effects like vocal-cord damage [57]. Second, in specific types of surgeries, e.g. intra-cranial, eye or abdominal surgery [57], profound NMB can be useful due to the need of complete immobility, or access to deep internal organs. Third, there is increasing evidence that residual NMB, i.e. the presence of some muscle relaxation in the post-operatory period, may adversely affect the patient recovery [89]. One way to avoid the presence of residual NMB is to titrate the amount of muscle relaxants to the desired NMB. For that, a quantitative and reliable measurement of the actual NMB level is needed.

The level of NMB is usually assessed by applying a supra-maximal electrical stimulus to a peripheral nerve e.g. the *adductor pollicis* muscle in the hand of the patient, and measuring the associated evoked muscular contraction. The supra-maximal stimulus is usually a current 25% above the one that evoked the maximal muscle contraction [89]. This current is usually applied trans-cutaneously using electrocardiogram (ECG) electrodes. The evoked responses can be quantified via the measurement of e.g. the mechanical response of the muscle (mechanomyography - MMG), the electrical response of the muscle (electromyography - EMG), the acceleration of the muscle response (acceleromyography - AMG), or the electrical response in a piezoelectric sensor attached to the muscle (kynemyography - KMG). See [55, 89] for further details.

Depending on the surgery and on the purpose of the NMB monitoring, there are several patterns available for nerve stimulation. Single twitch stimulation and train-of-four (TOF) stimulation are used whenever moderate NMB is required. While in the single twitch mode a single square wave supra-maximal stimulus is applied to the patient, in the TOF mode, a sequence of four stimuli with frequency 0.5Hz is applied. See e.g. [89] for a detailed comparison. Tetanic stimulation and post-tetanic count are often used whenever there is profound muscle relaxation, without any response from either single twitch or TOF stimulation, and may be used to predict the time to the reappearance of the first twitch of a TOF stimulation [57].

The NMB data used for the development of the work presented in this thesis came from a KMG-TOF/EMG-TOF stimulation of the *adductor pollicis* muscle. Mainly due to their ease of use, KMG and EMG are the standard monitoring techniques in the surgery rooms of the hospitals

where the data used for the work in this thesis were collected. The choice of the TOF follows the research line in anesthesia (Projects IDeA [2]/Galeno [4]) at Universidade do Porto, Portugal. A photo of the KMG NMB sensor used in the surgery room for data collection and test of the controllers in this thesis is shown in Fig. 2.1a. The electrical stimulation of the *adductor pollicis* muscle is performed via the two electrodes on the wrist of the patient, and the response is measured by the motion of the thumb. Unrelated with the NMB measurement, there is a finger oximeter placed on the middle finger of the patient.



(a) KMG NMB sensor (from surgery room of Hospital de Santo António, Porto, Portugal).

(b) BIS sensor (adapted from [3]).

Figure 2.1. Sensors that were used in the surgery room for data collection and test of the controllers that were developed in this thesis.

2.1.2 Hypnosis

Hypnosis encompasses both unconsciousness and amnesia. A patient under general anesthesia should hence not be able to process information from his or her surroundings and should not be able to retrieve memories from events that occurred during the surgery [1].

Hypnotics in clinical use today are inhalation agents, such as desflurane, isoflurane, and sevoflurane; and intravenous agents such as ketamine, etomidate, midazolan and propofol.

Inhalation anesthetics for surgical procedures are popular because of their ease of administration and the possibility for the clinician to reliably and directly assess their effects via the measurement of the end-tidal vapor concentrations of the inhaled agents [18].

Among the intravenous hypnotics, propofol has become the standard choice due to its fast distribution, metabolism and elimination [121]. At surgical concentration propofol has no intrinsic analgesic properties [18].

Its effect is however potentiated by e.g. remifentanil. See Section 3.4.1 for interaction models.

Propofol is the hypnotic drug used in the work presented in this thesis.

The majority of monitoring devices for hypnosis is based on the electroencephalogram (EEG) of the patient because it has been shown that there exists a reproducible correlation between the changes in the measured EEG and the hypnotic state of the patient [109]. Due to the complexity of those changes, most of the indices result from a combination of analysis of different components of the EEG. Examples of commonly used indices for both clinical and research purposes, are entropy-based [146], wavelet-based [161], the bispectral index (BIS) [47], and the auditory evoked potentials (AEP) [145], the latter being the only one that considers the evoked response of the brain to specific auditory stimuli in the calculations. Recently, a permutation entropy index that does not require long stationarity for the EEG sequences, unlike the bispectral- or entropy-based indices, is proposed in [71]. An up-to-date survey of the EEG-based depth of consciousness monitoring during general anesthesia is provided in [99].

The BIS is the index used in the daily clinical practice in the surgery rooms where the anesthesiologists of Project IDeA/Galeno [2, 4] work. A photo of the BIS sensor is shown in Fig. 2.1b.

2.1.3 Analgesia

Analgesia is related with the absence of pain. During general anesthesia the conscious experience of pain disappears due to the administration of hypnotics. Nevertheless, the surgical stimulation and tissue injury induce stress in the patients' body that may be reflected by changes in the heart rate, blood pressure and blood circulation. Severe surgical stress may delay post-operative recovery and may be associated with an increase in morbility [70]. The neural processes of encoding and processing these noxious stimuli are called nociception [82]. The physiological effects of nociception, and consequently surgical stress, can be attenuated with analgesics [70].

Typical choices of analgesics for general anesthesia belong to the family of opioids, of which sufentanil, alfentanil, fentanyl [122] and remifentanil are some examples.

Remifentanil is the analgesic used in the work presented in this thesis. It is the newest opioid available for use in humans and it differs from the other strong opioids in its rapid onset of duration due to a short blood-effect site equilibrium half-time and a rapid offset for all clinical effects [95].

Even though not having a direct hypnotic effect at clinical concentrations, when co-administered, remifentanil enhances the effect of propofol in a synergistic manner [95, 97].

Unlike the NMB, where an evoked response can be obtained to quantify the level of muscle relaxation of the patient, the anesthesiologist uses indirect physiological changes as tachycardia, hypertension, sweating, lacrimation [51] and actual movement of the patient to infer the patients' level of nociception and analgesia. Heart rate variablity [66], plethysmogram-based [60, 70] or the pulse transit time [130] have been investigated as potential measures to quantify the level of analgesia in patients under general anesthesia but none is yet widely accepted.

In the daily clinical practice in the surgery rooms where the data used for the development of the work presented in this thesis were collected, the BIS monitors are used. Therefore, and given its widespread use and acceptance, BIS signals were the outputs used to model the synergistic effect of both the hypnotic propofol and the analgesic remifentanil. In fact, some studies, e.g. [33], have shown that noxious stimuli influence the BIS baseline values, indicating that the BIS carries some information about the nociceptive path. Depth of anesthesia (DoA) is the word used in this thesis to define the effect of both analgesics and hypnotics in the patients under anesthesia.

Furthermore, it was assumed that the rocuronium- or atracurium-induced NMB and the propofol/remifentanil DoA are independent processes. Unlike some volatile agents, nothing has been proven indicating that intravenous hypnotics and analgesics influence the NMB level, and no strong evidence of a coupling at the physiological level between the NMB and DoA in humans exist [23, 32].

2.2 Temporal phases

A general anesthesia episode is commonly divided into three distinct temporal phases: induction, maintenance and recovery.

2.2.1 Induction

Induction starts with the administration of the chosen hypnotic or analgesic. Its duration is mainly dependent on how sensitive the patient is to these drugs. Before losing consciousness, the patient may cross a state of paradoxical excitation characterized by e.g. incoherent speech. Heart rate and blood pressure may also suffer considerable fluctuations during induction, and cardiovascular drugs may be administered to maintain

the hemodynamic stability. Tracheal intubation is usually performed at the end of induction, after the initial bolus of muscle relaxant. The boluses may be mathematically seen as pulses at different instants in time. As an example, for the case shown in Fig. 2.2, induction is until approximately minute twelve. The increase in the BIS around minute ten is a sign that the intubation is being performed. Since intubation is an invasive and stressful maneuver for the patient a transient increase in the BIS is usually observed, as shown in the upper plot of Fig. 2.2 at around minute ten.

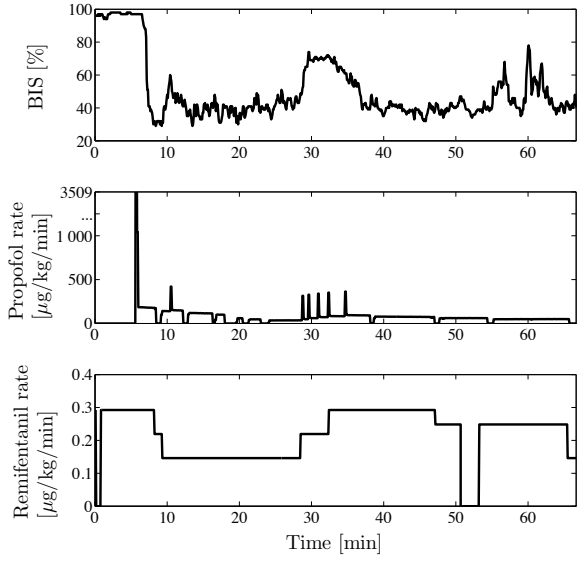


Figure 2.2. Data collected in the durgery room during general anesthesia. Upper plot: BIS. Middle plot: propofol rate administered by a TCI device. Bottom plot: remifentanil rate manually set in the syringe pump by the anesthesiologist.

2.2.2 Maintenance

Maintenance provides a sustained surgical anesthesia and usually comprises the administration of a combination of hypnotics and opioids, inhaled anesthetics, muscle relaxants, and cardiovascular drugs. Ventilatory and thermoregulatory support should also be provided. During the maintenance period, movement, changes in the heart rate, blood pressure and in the NMB and EEG-derived indices are among the clinical signs used to monitor the level of general anesthesia.

The processes behind induction and maintenance of anesthesia are, however, still not completely understood. See e.g. [42] for further details.

2.2.3 Recovery

Recovery is considered to start when the administration of anesthetics is stopped and to end when consciousness and normal physiological functions are regained. If the patient still presents considerable muscle relaxation, reversal agents may be used in order to hasten recovery and enable spontaneous ventilation. This is the case in Fig. 2.3, where atropine and neostigmine are administered to reverse the NMB. The patient is extubated as soon as he or she shows clinical signs of wakefulness.

2.3 Administration regimens

Depending on the type of hypnotics and analgesics that are chosen, the anesthetic protocols may be classified as: completely inhalational, balanced or total intravenous anesthesia (TIVA).

While completely inhalational anesthesia may be an option for surgeries with limited noxious stimulation, whenever the surgical procedure is likely to induce painful stimulation to the patients, an intravenous analgesic is usually co-administered. This constitutes a balanced anesthesia protocol. Most recently, due to the availability of intravenous drugs with more rapid onset and shorter recovery profiles than their inhalational counterparts, TIVA has become a common choice.

The work presented in this thesis deals with TIVA due to the fact that the hypnotic propofol, the analgesic remifentanil (and the muscle relaxants atracurium and rocuronium) are intravenously administrated.

2.3.1 Manual

The standard practice for administration of intravenous drugs in general anesthesia is via intermittent bolus or manual adjustment of the flow rate of the drugs being administered by the syringe pumps. This approach is reactive in the sense that, whenever the anesthesiologist perceives some change in the patient's general condition, he or she acts accordingly by changing the rate in the syringe pumps or by administering a bolus. The anesthesiologist "calculates" the magnitude of the change of the administered drug based on his or her previous clinical experience, on the signals that all the monitors provide to the medical staff, and on the drugs' guidelines and published pharmacokinetics/pharmacodynamics (PKs/PDs). Further, the verbal feedback given

by the surgeons and other medical staff on the progress of the surgery is also taken intro account in the decision. One example of a real case where three bolus of the muscle relaxant rocuronium were administered in shown in Fig 2.3. The bottom plot of Fig 2.2 shows one real case where the rate of the analgesic remifentanil to be administered to the patient was manually set in the syringe pump by the anesthesiologist.

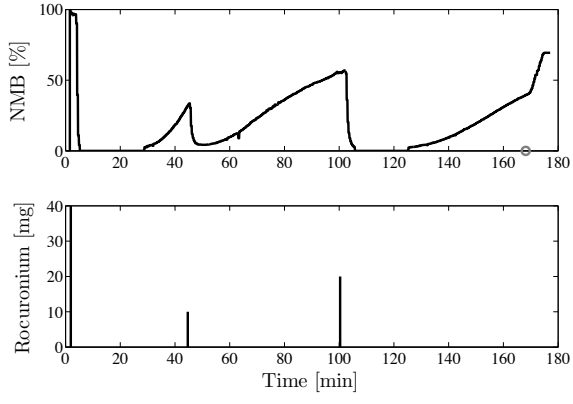


Figure 2.3. Data collected in the durgery room during general anesthesia, with manual administration of the muscle relaxant rocuronium. Upper plot: First twitch of a TOF stimulation normalized by the reference twitch, quantifying the NMB level. Bottom plot: rocuronium bolus. The 'o' on the x-axis of the upper plot marks the time when a bolus of atropine and neostigmine is intravenously administered to fasten the recovery of the NMB.

In most of the cases the titration of the individualized amount of drug is time-consuming because the anesthesiologist needs to see the effect of the change in the administered drug to further correct it. Therefore this manual administration results in a DoA or NMB that oscillates above and below the desired level [18]. In all cases, the anesthesiologist has the important role of anticipating the effect that the surgeons' actions might induce in the patients' anesthetized state. For instance, whenever the anesthesiologist perceives or is told that a possibly noxious stimulus is to be applied to the patient he or she increases the amount of hypnotic and/or analgesic, so that it is less likely that the patient "suffers" from the surgeons' action.

As summarized in [134], the anesthesiologist has the combined role of estimator of the state of the system and feedback controller, and must have a predictive role with respect to e.g. foreseeable disturbances and reference changes.

2.3.2 Target-controlled infusion

The knowledge about the drugs distribution and metabolism was firstly exploited in the development of the target-controlled infusion (TCI) syringe pumps. The first TCI pump, Diprifusor, was proposed in 1996 for propofol [48] and since then several other manufacturers followed.

The TCI concept is a hybrid between manual and model-based closed-loop administration for the case of known parameters. The anesthesiologist, based on the status of the patient and on the progress of the anesthetic procedure, sets the target concentration (reference) and the TCI device calculates the corresponding drug profile to be administered. The target can be either set at the plasma or the effect concentration.

The middle plot of Fig 2.2 shows one real case where the rate of the hypnotic propofol was changed by the TCI device. The peaks in the administered dose are consequence of manual increases in the target effect concentration of propofol. The time intervals during which the administration stops are consequence of a decrease in the target effect concentration of propofol.

The parameters of the linear multi-compartmental PK(/PD) models used by the TCI devices are derived from population studies and depend on the patient's gender, age, weight and height. See e.g. [87, 119, 121] for details. Since no measurements of the actual concentrations are made, TCI are referred to as open-loop [5]. Consequently, any modeling errors and disturbances have to be compensated for manually by re-setting the target concentration of the drug in the TCI devices.

Although some studies demonstrate the clinical advantages of TCI [115], according to [24, 77] the effectiveness of TCI-based anesthesia when compared with manual infusions still needs to be proven. The relatively large inter-individual error in predicting the PK/PD of patients may be considered a limiting factor for the use of TCI in anesthesia [90, 111, 121].

2.3.3 Closed-loop

According to [14], the discovery of new improved anesthetic drugs and the increasing understanding of their PK and PD highly contributed to the reduction of anesthesia-related mortality over the past decades. While several studies, e.g. [14, 112, 117], indicate that one way to standardize and further improve the safety of drug delivery in anesthesia is to use closed-loop controllers, the lack of evidence that closed-loop controllers are safe in all surgical conditions is what is holding back the development and systematic test of automatic closed-loop strategies in anesthesia.

Also, several of the core features of drug delivery in anesthesia constitute major challenges for the development of automatic closed-loop controllers.

First, the patients' responses to the administration of anesthetics are intrinsically nonlinear and time-varying. The nonlinear nature results from a sigmoidal relationship between the drug concentration at the effect site and the measured effect. The time-varying profile is mainly the consequence of several noxious stimulations, the change in the tolerance to drugs related to e.g. receptor wear-off, unmodeled interactions between drugs or other major changes in the patient, e.g. blood losses, that may occur during the surgery. Consequently, models should preferably be established individually and in real-time [148].

Secondly, the nonnegative nature of the system also needs to be accounted for. The whole system is, by definition, positive. Since no drugs can be removed from the patients once administered, the variables to be controlled, i.e. drugs rates, are intrinsically nonnegative. Moreover, all the syringe pumps that are available in the market impose an upper limit in the drug rate they can administer. This may be tackled by introducing actuator saturations. A good example where actuator saturations have to be accounted for in the controller design is the case of adaptive controllers, which continue to adapt even when the system is saturated, leading to windup effects and unacceptable transients after saturation [53].

Thirdly, the limited amount of real-time data and the poor excitation properties of the input signals constitute issues to take into account in the design of the whole control strategy. These are the two major reasons that triggered and justified the development of the research work presented in this thesis. The poor excitation properties of the input signals are exemplified by the drug rates in Figs. 2.3 and 2.3. On the one hand, at the beginning of a general anesthesia procedure, when no substantial data from the patient are available, the knowledge about the individual patient's response to the anesthetic is insufficient to initialize and tune the control algorithms. On the other hand, due to the monitoring devices or other restrictions from the clinical protocol, the sampling frequency of the signals of interest is far from ideal and usually quite slow. Moreover, due to medical constraints, the inputs are not allowed to be chosen for best performance of identification experiments [148].

Fourthly, the accuracy of closed-loop control strongly depends on the reliability of the controlled variable. In contrast to several other physiological variables collected during general anesthesia, e.g. the heart rate, the blood pressure or the NMB, no direct measures exist to evaluate the hypnotic and analgesic components of anesthesia. Further, the highly busy surgery room environment, in which several members of the staff act on the patient simultaneously, generate disturbances that are unpredictable and difficult to characterize. The difference in surgical protocols should also be taken into consideration in a disturbance rejection framework.

3. Mathematical modeling

Mathematical models of dynamic systems are useful in many areas and applications. According to [133] there are basically two types of mathematical models: first principles models and system identification models.

First principles models are derived from laws of physics and are useful to e.g. obtain deep insight on the process. The idea is often to describe the whole behavior of a system by coupling together accurate sub-system descriptions of the process.

System identification models are estimated from measured data. In this case it is the observation of the system dynamics that leads to the model. An important decision while performing system identification is whether the models should be parametric or non-parametric. Parametric models may be seen as mappings from the recorded data to a finite-dimensional estimated parameter vector. Non-parametric models include curves, tables or functions that cannot (explicitly) be represented by a finite-dimensional parameter vector. Impulse responses or frequency diagrams are examples of non-parametric models.

In anesthesia the efforts from the research and medical community aim at the development of automatic controllers for individualized drug delivery. Preliminarily to the controller design, a good model for the behavior of the system, from an input-output perspective, has to be obtained. This fact motivates the approach used for system identification in this work. The use of continuous-time parametric models and methods is justified by the poor excitation properties of the input signals, i.e. the drugs that are administered, and the fact that the end-goal of the modeling is the design of model-based controllers.

3.1 Nonlinear models and system identification methods

In parametric system identification it is necessary to choose a class of models before making the appropriate choices in terms of e.g. model order or a particular structure within the selected class [133]. The goal is usually to find descriptions that are flexible enough to cover the relevant phenomena, allowing at the same time the inclusion of some physical insight [79]. Moreover, the parsimony principle of system identification states that out of two or more competing models which both explain the

data well, the model with the smallest number of independent parameters should be chosen [133].

The most commonly used nonlinear continuous-time model structures are special cases or closely related to state-space models [108], as described by

$$\begin{aligned} \dot{x}(t) &= f(x(t), u(t), \theta) + g(x(t), \theta)v(t), \\ y(t) &= h(x(t), u(t), \theta) + e(t), \end{aligned} \tag{3.1}$$

where $x \in \mathbf{R}^n$, $u \in \mathbf{R}^k$, and $y \in \mathbf{R}^p$ are state, input and output vectors; $\theta \in \mathbf{R}^m$ is the parameter vector; f is a nonlinear vector function that maps $\mathbf{R}^n \times \mathbf{R}^k \times \mathbf{R}^m$ into $\mathbf{R}^n$; g is a nonlinear vector function that maps $\mathbf{R}^n \times \mathbf{R}^m$ into $\mathbf{R}^n$; h is a nonlinear vector function that maps $\mathbf{R}^n \times \mathbf{R}^k \times \mathbf{R}^m$ into $\mathbf{R}^p$; and v and e are process and measurement disturbances, respectively, with rational spectral densities $Ev(t)v^T(t') = \Pi(\theta)\delta_{t,t'}$ and $Ee(t)e^T(t') = \Lambda(\theta)\delta_{t,t'}$, respectively.

3.1.1 Control-affine models

Control-affine models restrict the nonlinear vector map f in (3.1) to the special form

$$f(x(t), u(t), \theta) = \Phi(x(t), \theta) + \Gamma(x(t), \theta)u(t). \tag{3.2}$$

The structural restriction on f naturally limits the class of dynamic phenomena that might be represented by control-affine models. Nevertheless, in [108] it is shown that this class is quantitatively rich enough to describe e.g. chaotic dynamics. It is also suitable for e.g. feedback linearizing control [68, ch.13].

3.1.2 Restricted nonlinear ordinary differential equation models

One class of nonlinear ordinary differential equation (ODE) models uses a restricted parameterization, where only one component of the right hand-side of the ODE is parameterized with coefficients of a multi-variable polynomial. The remaining components consist of a set of integrators [153, 154].

The model can be formulated as

$$\begin{pmatrix} x_1^{(1)} \\ \vdots \\ x_{n-1}^{(1)} \\ x_n^{(1)} \end{pmatrix} = \begin{pmatrix} x_2 \\ \vdots \\ x_n \\ f_n\left(x_1, \ldots, x_n, u_1, \ldots, u_1^{(n_1)}, \ldots, u_k, \ldots, u_k^{(n_k)}, \theta\right) \end{pmatrix},$$

$$\begin{pmatrix} y_1 \\ \vdots \\ y_p \end{pmatrix} = \begin{pmatrix} h_1\left(x_1, \ldots, x_n, u_1, \ldots, u_k^{(n_k)}, \theta\right) \\ \vdots \\ h_p\left(x_1, \ldots, x_n, u_1, \ldots, u_k^{(n_k)}, \theta\right) \end{pmatrix}, \tag{3.3}$$

where the superscript $^{(k)}$ denotes differentiation k times. The other variables are defined as in (3.1). The time dependency of the states and of the input in (3.3) is dropped for the sake of notational simplicity.

The discretization of the model in (3.3) can be done via Euler forward discretization as in [152]. Successful examples of the implementation of system identification based on (3.3) include [26, 141].

3.1.3 Discrete-time nonlinear difference equations

Apart from the models obtained via discretization of the continuous-time models mentioned above, the structures based on difference equations are other important examples of nonlinear models.

A nonlinear generalization of the autoregressive moving average with exogenous signal (ARMAX) model as

$$A(q^{-1})y(t) = B(q^{-1})u(t) + C(q^{-1})e(t) \tag{3.4}$$

is given by the nonlinear autoregressive moving average with exogenous signal (NARMAX) model [30]

$$y(t) = F\left(y(t-1), \ldots, y(t-n_y), u(t-1), \ldots \right. \\ \left. \ldots, u(t-n_u), e(t-1), \ldots, e(t-n_e)\right), \tag{3.5}$$

where y is the output; u is the input; e is white noise; q^{-1} is the backward shift operator; $A(q^{-1})$, $B(q^{-1})$ and $C(q^{-1})$ are polynomials and $F(\cdot)$ is an arbitrary nonlinear function.

Similarly, the nonlinear autoregressive with exogenous signal (NARX) and nonlinear finite impulse response (NFIR) models are the nonlinear equivalents of autoregressive with exogenous signal (ARX) and finite impulse response (FIR) models, respectively. See e.g. [108, 131].

3.1.4 Block-oriented models

Block-oriented models exploit the interaction between linear time-invariant (LTI) dynamic systems and static nonlinear elements [15]. The LTI and static nonlinear blocks may be interconnected in different ways e.g. in series, in parallel or as feedback, which makes the block-oriented models flexible enough to capture the dynamics of many real systems.

The simplest structures are composed by two blocks in cascade.

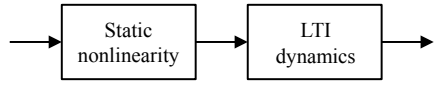
In the Hammerstein model, the nonlinearity is located at the input (Fig. 3.1a). A list of examples where Hammerstein models are used can be found in [15]. Existing methods in the literature for identifications of Hammerstein models comprise the over-parameterization method, frequency domain methods, and iterative methods. See e.g. [16] for more details.

In the Wiener model, the nonlinearity is located at the output (Fig. 3.1b). Cases where there exists saturation in the sensors that measure the system output are usually treated as Wiener models [152]. Even though apparently similar, it is easier to perform system identification for the Hammerstein model than for the Wiener model. The reason is that the Hammerstein model can be re-parameterized as a linear MISO model [105]. The Wiener model is used in this thesis. A reason why existing recursive prediction error methods (RPEMs) are not used is that the algorithms of e.g. [151] are generally parameterized. The discrete-time pole-zero dynamics and the piecewise-linear nonlinear model contain too many parameters to work well in anesthesia applications.

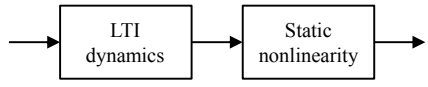
A cascade combination of a Hammerstein and a Wiener model yields two different model structures depending on the positions of the blocks. In the case where two static nonlinearities are located at the input and at the output, with a LTI system between them, the model is Hammerstein-Wiener (Fig. 3.1c). If the nonlinearity is enclosed by two LTI blocks, the model is Wiener-Hammerstein (Fig. 3.1d).

3.1.5 Artificial neural networks

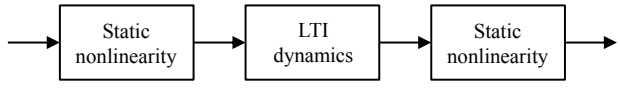
An artificial neural network consists of many dynamic artificial neurons or nodes arranged in layers, operating in parallel [31]. Each neuron receives input from a number of other units or external sources, weighs each input and adds them up [72]. The choice of a suitable network architecture can be done by applying methods of model assessment and selection, such as cross-validation. Once the architecture considered to be the best is selected, the corresponding network is trained. This corresponds to the choice of the a set of values for the weights which define the strength of connection between the nodes. The identification can be performed by solving an optimization problem based on the error be-



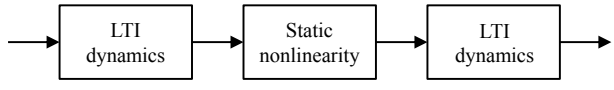
(a) Hammerstein model.



(b) Wiener model.



(c) Hammerstein-Wiener model.



(d) Wiener-Hammerstein model.

Figure 3.1. Block-oriented model structures. In a general framework the arrows represent vector-valued entities.

tween the model and the collected data. After this step, the resulting network can be applied to new data to obtain an estimate of the unknown parameterization. The major drawback of this structure for the identification is that the number of parameters increases considerably with the number of nodes.

3.1.6 Bayesian approaches

In the Bayesian approaches, the aim is to construct the posterior probability density function (pdf) of the state based on the available information, including the sequence of received input-output measurements. Since this pdf embodies all available statistical information, it may be regarded to be the complete solution to the estimation problem. Whenever an estimate of the pdf is required every time a measurement is received, a recursive filter is needed. Such recursive filters consist of two stages: prediction and update. The prediction stage uses the system model to predict the state pdf forward. Since the state is usually subject to unknown disturbances, prediction generally deforms and broadens the state pdf. The update stage uses the latest measurement to modify (typically tightening) the prediction pdf. This may be achieved using Bayes theorem [113].

A common assumption for the recursive filtering problems is that of linearity and Gaussianity of the process and observation noises. This is the case for the Kalman filter [132]. The extended Kalman filter (EKF) applies the standard linear Kalman filter algorithm after linearization of the nonlinear system around the current estimates [132]. While the Gaussianity assumption and linearization make the EKF simple to implement and fast to execute, the EKF suffers from an inherent inability to model truly non-Gaussian posterior densities. One possible approach to circumvent this weakness is by the use of sequential Monte Carlo (SMC) methods [37]. The particle filter (PF) methods are recursive implementations of the SMC samplers that offer approximate solutions for the pdf calculations. The key idea is to represent the required posterior pdf by a set of random samples with associated weights and to compute estimates based on these samples and weights. As the number of samples becomes very large, this Monte Carlo characterization becomes an equivalent representation of the posterior pdf. The accuracy of the PF is hence limited by the available computational resources [120] and the accuracy of the underlying model. Since the PF is expensive in terms of computational requirements, it should only be used when problems are highly nonlinear and the conventional methods derived from the Kalman filter do not produce satisfactory results.

By e.g. state augmentation, the Bayesian methods provide a formal treatment of time-varying parameters problem, thus providing a good solution for parameter tracking problems [81]. This capability motivated the use of the EKF and the PF for parameter estimation and tracking in this thesis. A comparison of performances between these two methods for the case of the NMB is presented in Paper III.

3.2 Identifiability

For the discussion on identifiability, assume that there is a true system $\mathcal{S}$ which is nonlinear and continuous-time. The general state-space description of the system $\mathcal{S}$ may hence be

$$\begin{aligned} \dot{x}_s(t) &= f_s(x_s(t), u(t)) + g_s(x_s(t))v_s(t), \\ y_s(t) &= h_s(x_s(t), u(t)) + e_s(t), \end{aligned} \tag{3.6}$$

where y_s is the system output; u is the system input; x_s is the state of the system; $f_s(\cdot)$, $g_s(\cdot)$ and $h_s(\cdot)$ are nonlinear functions; and v_s and e_s are process and measurement disturbances, respectively, with rational spectral density $Ev_s(t)v_s^T(t') = \Pi_s\delta_{t,t'}$ and $Ee_s(t)e_s^T(t') = \Lambda_s\delta_{t,t'}$, respectively.

The set

$$\begin{aligned} D_T(\mathcal{S},\mathcal{M}) =& \{\theta \mid f_s(x_s(t),u(t)) \equiv f(x(t),u(t),\theta), \\ & g_s(x_s(t)) \equiv g(x(t),\theta),\ \ h_s(x_s(t),u(t)) \equiv h(x(t),u(t),\theta), \\ & \Pi_s \equiv \Pi(\theta),\ \Lambda_s \equiv \Lambda(\theta)\} \end{aligned} \tag{3.7}$$

consists of those parameter vectors for which the model structure given by (3.1) gives a perfect description of the true system $\mathcal{S}$ [133, p. 162]. Three situations can occur:

- The set $D_T(\mathcal{S},\mathcal{M})$ is empty, which means that no perfect model for the true system exists, regardless of the parameter values. This is the case of under-parameterization, i.e. the model does not possess enough parameters or the right structure to describe the true system behavior. This is usually the case in practice, where modeling errors are normally present.
- The set $D_T(\mathcal{S},\mathcal{M})$ consists of one point, i.e. the true parameter vector, denoted by θ_0. This is the ideal case.
- The set $D_T(\mathcal{S},\mathcal{M})$ consists of several, possibly infinitely many points, this meaning that there are several models within the model set that perfectly describe the system. This is the case of over-parameterization.

System identification is focused around the determination of $D_T(\mathcal{S},\mathcal{M})$ from the inputs u and the measured outputs y. In general this may not be possible [110], since $D_T(\mathcal{S},\mathcal{M})$ may be very complicated.

A priori or structural identifiability assesses whether the parameters can be uniquely globally or locally determined from input-output observations, typically under the assumption that the input is persistently exciting (pe) [80, 110, 116]. Structural identifiability is a prerequisite and necessary condition for any estimation procedure to allow a unique recovery of the model parameters from input-output data [110]. While for linear models a variety of techniques exist [133], assessing structural identifiability for nonlinear models, especially the ones of biomedical/biological systems, is far more involved [19].

Practical or data-based identifiability can only be assessed using experimental (or simulated) data, and depends on the specific measurements and properties of the input signals [116].

The idea of identifiability can, according to [133], be formalized as follows. Denote by $\hat{\theta}(N;\mathcal{S},\mathcal{M},\mathcal{I},\mathcal{H})$ the estimate resulting from the application of an identification method $\mathcal{I}$ to a parametric model structure $\mathcal{M}$. Hence, the estimate depends not only on $\mathcal{I}$ and $\mathcal{M}$ but also on the number of data points N, the true system $\mathcal{S}$ and the experimental conditions $\mathcal{H}$.

The system $\mathcal{S}$ is said to be (data-based) system identifiable under $\mathcal{M}$, $\mathcal{I}$ and $\mathcal{H}$, abbreviated SI($\mathcal{M}$, $\mathcal{I}$, $\mathcal{H}$) [133, p. 167], if

$$\hat{\theta}(N; \mathcal{S}, \mathcal{M}, \mathcal{I}, \mathcal{H}) \to D_T(\mathcal{S}, \mathcal{M}), \text{ as } N \to \infty \tag{3.8}$$

with probability one. For SI($\mathcal{M}$, $\mathcal{I}$, $\mathcal{H}$) it is required that the set $D_T(\mathcal{S}, \mathcal{M})$ in (3.7) is non-empty. If $D_T(\mathcal{S}, \mathcal{M})$ contains more than one point, (3.8) should be interpreted as

$$\lim_{N\to\infty} \inf_{\theta \in D_T(\mathcal{S},\mathcal{M})} \|\hat{\theta}(N; \mathcal{S}, \mathcal{M}, \mathcal{I}, \mathcal{H}) - \theta\| = 0. \tag{3.9}$$

Further, the system is parameter identifiable under $\mathcal{M}$, $\mathcal{I}$ and $\mathcal{H}$, abbreviated PI($\mathcal{M}, \mathcal{I}, \mathcal{H}$) [133, p. 167], if it is SI($\mathcal{M}, \mathcal{I}, \mathcal{H}$) and $D_T(\mathcal{S}, \mathcal{H})$ consists of exactly one point. Thus, if the system is PI($\mathcal{M}, \mathcal{I}, \mathcal{H}$), the parameter estimates $\hat{\theta}$ will be unique and consistent for large values of N.

Data-based identifiability was addressed in the work presented in this thesis for model structure selection, in Paper IV. The experimental conditions, here denoted by $\mathcal{H}$, concern sampling rates and the type of input that is used.

3.3 Input requirements

3.3.1 Linear systems

When input signals for identification of linear systems are chosen, the emphasis is usually on the frequency contents of the signal. According to [133], an input signal u is said to be pe of order n if the limit

$$r_u(\tau) = \lim_{N\to\infty} \frac{1}{N} \sum_{t=1}^{N} u(t+\tau) u^T(t) \tag{3.10}$$

exists, and if the matrix

$$R_u(n) = \begin{pmatrix} r_u(0) & r_u(1) & \dots & r_u(n-1) \\ r_u(-1) & r_u(0) & & \vdots \\ \vdots & & \ddots & \\ r_u(1-n) & \dots & & r_u(0) \end{pmatrix} \tag{3.11}$$

is positive definite. A necessary condition for consistent estimation of an n-th order pole-zero linear (noisy) system is that the input signal is pe of order $2n$ [133, p. 121].

For white noise input with zero mean and variance σ^2, $r_u(\tau) = \sigma^2\delta(\tau)$ and $R_u(n) = \sigma^2 I_n$, which is always positive definite. Thus, white noise

is pe of any order. Similarly, for a PRBS that shifts between the values a and $-a$, with period M,

$$r_u(\tau) = \begin{cases} a^2, & \tau = 0, \pm M, \pm 2M, \dots \\ -a^2/M, & \text{elsewhere.} \end{cases} \tag{3.12}$$

and

$$R_u(n) = \begin{pmatrix} a^2 & -a^2/M & \dots & -a^2/M \\ -a^2/M & a^2 & & \vdots \\ \vdots & & \ddots & \\ -a^2/M & \dots & & a^2 \end{pmatrix}. \tag{3.13}$$

Therefore a PRBS is pe of order M [133, p.125]. For $a^2 = \sigma^2$ and M large, for moderate values of τ, the PRBS and white noise have similar covariance properties. Hence the PRBS is commonly chosen as input for identification of linear systems.

3.3.2 Nonlinear systems

When nonlinear models are identified, the signal levels need to be high enough for the nonlinear effects to be significant. This means that the signal-to-noise ratios can in many cases be expected to be at least as good as when linear models are identified [152]. Moreover, it should be noted that even though signal levels can often be increased above the levels needed for a linear system identification, the constraints may prevent that. This is e.g. the case in many biomedical applications where patient safety affects the signal level. There are also cases where nonlinear effects are important for low signal levels, e.g. backlash and stick friction [68].

In cases where the input signal to the system cannot be freely selected, conventional parametric methods may offer a more widely applicable alternative than many of the non-parametric algorithms. Reasons include the fact that non parametric models are often "re-parameterized" in practice when applied, and then the number of parameters often becomes high.

The theoretical properties that need to be fulfilled in order to secure a well-behaved algorithmic performance of parametric identification algorithms have been determined for example for the case of Wiener models. For Wiener models the input signal requirement that is related to the linear block is one of persistency of excitation of high enough order [150, 151]. Regarding the nonlinear block, the input signal needs to be such that the output from the linear block of the Wiener model has signal energy in the whole amplitude range of the static nonlinearity [151].

In this sense, a PRBS provides bad conditions for the identification of e.g. Wiener systems [150, pp.151-153].

Input signal design is hence related to black-box system identification. The work in [65] exemplifies the success of the application of input design techniques for parameter estimation of the human smooth pursuit mechanism system from eye-tracking data when modeled as a Wiener model. Results show that the input design reduces the variance of the parameter estimates, which is desirable to diagnose diseases where this pursuit mechanism is compromised.

3.4 Effect of intravenous anesthetics

One of the main problems in developing drug delivery systems is the lack of accurate mathematical models for characterizing the dynamic effect of the administered drugs on the measured physiological variables [53]. System nonlinearities, model parameter variations from patient to patient, denoted inter-patient variability, or within the same patient under different conditions, denoted intra-patient variability, are big challenges for successful modeling.

3.4.1 Standard models

The standard models for the effect of intravenous drugs in anesthesia were first developed based on collected blood samples at different time instants after administration of the drugs. Based on that insight, the path from the administered amount of drug to the measured effect is divided into two parts. First, the pharmacokinetics (PKs) describes what the body does to the drug and concerns the drug distribution and metabolism in the blood stream. The input to the PK model is the amount of drug administered and the output is the drug plasma concentration. Secondly, the pharmacodynamics (PDs) describes what the drug does to the body. The input to the PD model is the plasma concentration and the output is the physiological variable that quantifies the effect of the drug. Supported by experimental evidence, it is natural to model the effect of drugs in anesthesia by two cascaded blocks.

Due to the fact that the majority of the PK of the drugs consists of linear dynamics, and the PDs behaves as a static nonlinearity, a Wiener model (Fig. 3.1b) has become a natural choice to model the effect of intravenous anesthetics [17, 36].

In what the PKs is concerned, the distribution of the drugs in the body depends on several transport and metabolic processes. Compartmental models [49] capture this behavior by considering the body divided in com-

partments that exchange positive amounts of drugs between each other. Assuming an instantaneous mixing of the drug in each compartment, conservation laws are used to derive the associated dynamic equations. Two or three compartmental (mammilary) models [49] are the ones most commonly used to describe the PKs of muscle relaxants, hypnotics and analgesics.

Since the blood plasma is not the effect site of any of the anesthetics that are used in this work, a delay between the concentrations of the drugs and observed effect exists. The indirect link models [36] model this delay by connecting an additional virtual effect compartment to the central (plasma) compartment. In order to ensure that the equilibrium of the PKs is not affected, it is assumed that this virtual compartment has negligible volume. This constitutes the linear part of the PD model.

At the effect site, the way anesthetics act has a more complex characterization than the distribution of the anesthetics in the body. Empirical models are therefore used to describe this part of the PDs [36]. The classic and most commonly used description is the Hill function, a sigmoid static nonlinear function relating the effect concentration of the drug with its observed effect [36, 58].

Neuromuscular blockade

The standard models of the linear dynamics of non-depolarizing muscle relaxants in the NMB assume the existence of two or three compartments (central and peripheral) communicating with each other, and an effect compartment [88, 149]. Using mass conservation laws, and after some transformations from micro- to macro-rate constants, a possible state-space realization of the linear part of the Wiener model for the NMB is

$$\begin{bmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \\ \dot{c}(t) \\ \dot{c}_e(t) \end{bmatrix} = \begin{bmatrix} -\lambda_1 & 0 & 0 & 0 \\ 0 & -\lambda_2 & 0 & 0 \\ \lambda & \lambda & -\lambda & 0 \\ 0 & 0 & 1/\tau & -1/\tau \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \\ c(t) \\ c_e(t) \end{bmatrix} + \begin{bmatrix} a_1 \\ a_2 \\ 0 \\ 0 \end{bmatrix} u_a(t). \tag{3.14}$$

Here the input $u_a(t)$ [μg kg^{-1} min^{-1}] is the administered rate of the muscle relaxant, and the output is its effect concentration $c_e(t)$ [μg ml^{-1}]. The $x_i(t)$, {i=1,2} are state variables such that the atracurium plasma concentration $c_p(t)$ [μg ml^{-1}] equals $x_1(t) + x_2(t)$. The a_i [kg ml^{-1}], λ_i [min^{-1}], {i=1,2} are the patient-dependent parameters in the PK model.

The plasma concentration of the muscle relaxant and its effect concentration $c_e(t)$ are related by the linear PDs as given in the two last rows of (3.14). The state variable $c(t)$ is an intermediate variable, and λ [min^{-1}] and τ [min] are patient-dependent parameters.

The standard models developed for atracurium [149] do not consider the last row of (3.14). As shown in [74], the inclusion of this equation corresponds to a first order approximation of the τ delay and allows a better replication of the observed experimental responses.

The PD nonlinearity relates the effect concentration $c_e(t)$, impossible to measure in the clinical practice, to the effect of the drug as quantified by the measured NMB $y(t)$ [%]. It is usually modeled by the Hill function [149] as

$$y(t) = \frac{100\, C_{50}^{\gamma}}{C_{50}^{\gamma} + c_e^{\gamma}(t)}\,, \tag{3.15}$$

where C_{50} [μg ml^{-1}] and γ (dimensionless) are also patient-dependent parameters.

The patient-dependent parameters in the NMB standard model are hence the following eight: a_1, a_2, λ_1, λ_2, λ, τ, C_{50}, and γ.

Figure 3.2 shows the NMB of sixty patients after the administration of the standard 500 μg kg^{-1} bolus of atracurium during the induction phase. For the same input dose, the time to reach the minimum NMB value in the population varies between three and fifteen minutes. This exemplifies the inter-patient variability of this system.

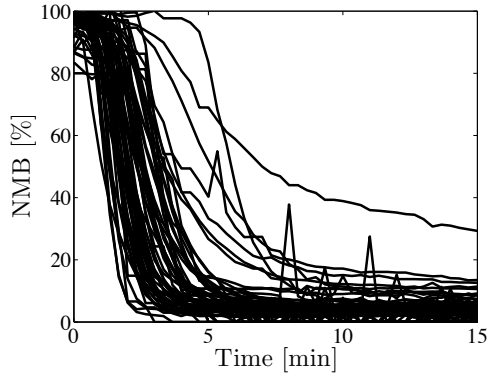


Figure 3.2. NMB responses of sixty patients after the administration of the standard 500 μg kg^{-1} bolus of atracurium during the induction phase. Data collected with EMG sensor in the surgery room.

Depth of anesthesia

For both propofol and remifentanil, a three-compartment mammilary model is normally used to explain the linear distribution of each drug in the different theoretical compartments of the human body [43, 96]. By direct deduction from mass balances between compartments, and

assuming that for each compartment i at time t, a concentration $c_i(t)$ [mg ml^{-1}] of drug is present, the state space representation that is commonly used becomes

$$\begin{bmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \\ \dot{x}_3(t) \\ \dot{c}_e(t) \end{bmatrix} = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ k_{e0} & 0 & 0 & -k_{e0} \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \\ c_e(t) \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} u(t)\,. \tag{3.16}$$

Here $u(t)$ [mg ml^{-1} min^{-1}] is the drug infusion rate (either propofol or remifentanil), k_{10} [min^{-1}] is the clearance of the drug from the compartment 1, k_{e0} [min^{-1}] is the clearance of the drug from the effect compartment, and k_{ij} [min^{-1}] are transfer coefficients from compartment i to compartment j. The effect concentration of the drug $c_e(t)$ [mg ml^{-1}] is given by the last row in (3.16). In clinical practice, neither $x_i(t)$ nor $c_e(t)$ can be measured.

The parameters k_{ij} in (3.16) are usually guessed based on population model distributions. See e.g. [87] and [119] for propofol and e.g. [96] for remifentanil.

The joint effect of propofol and remifentanil in the DoA is nonlinear and supra-additive [97]. The potency of the drug mixture is modeled as

$$\phi = \frac{U_p(t)}{U_p(t)+U_r(t)}\,, \tag{3.17}$$

where, by definition, ϕ ranges from 0 (remifentanil only) to 1 (propofol only). Here the subscript "p" refers to propofol and the subscript "r" refers to remifentanil.

To calculate (3.17) both effect concentrations $c_{ep}(t)$ and $c_{er}(t)$ are first normalized with respect to their concentration at half the maximal effect (C_{50p} and C_{50r}, respectively) as

$$U_p(t) = \tfrac{c_{ep}(t)}{C_{50p}}\,,\;\; U_r(t) = \tfrac{c_{er}(t)}{C_{50r}}\,. \tag{3.18}$$

The nonlinear concentration-response relationship for any ratio of the two drugs can then be described by the generalized Hill function

$$y(t) = \frac{y_0}{1+\left(\frac{U_p(t)+U_r(t)}{U_{50}(\phi)}\right)^{\gamma}}, \tag{3.19}$$

where y_0 is the effect at zero concentration, γ controls the steepness of the nonlinear concentration-response relation, and $U_{50}(\phi)$ is the number of units associated with 50% of the maximum effect of both drugs at ratio ϕ. In [97] the quadratic polynomial

$$U_{50}(\phi) = 1 - \beta\phi + \beta\phi^2 \tag{3.20}$$

was proposed for the expression of $U_{50}(\phi)$. The parameters C_{50p}, C_{50r}, γ, β and y_0 in (3.18)-(3.20) are patient-dependent.

The patient-dependent parameters in the DoA standard model are hence the following seventeen: k_{10p}, k_{12p}, k_{13p}, k_{21p}, k_{31p}, k_{e0p}, for propofol, k_{10r}, k_{12r}, k_{13r}, k_{21r}, k_{31r}, k_{e0r}, for remifentanil, and C_{50p}, C_{50r}, γ, β and y_0.

3.4.2 Minimally parameterized models

For the work presented in this thesis, parametric nonlinear Wiener models were chosen. The reason for this is threefold.

First, due to physiologic reasons and monitoring restrictions of the medical instrumentation in the surgery room, the amount of available data are limited by the maximum sampling rates allowed. Parametric structures in general enable the use of a small number of parameters. This is advantageous given the poor excitatory profile of the input signals in the application at hand, and considering that the end-goal of modeling in this application is the development of closed-loop controllers. The models are hence parameterized in terms of a small set of parameters that define models of the blocks of the Wiener structure. This is particularly important because in this application, the input signals cannot be freely chosen to enable a better identification. Instead, they are subject to the clinical protocols and recommended ranges.

Secondly, as explained in detail in Papers I, II and IV, the linear dynamics of the standard models is, considering the data available, "practically" over-parameterized. Further, in some cases, the system experiences close to zero-pole cancellation (see Paper I), which indicates a need for model reduction while keeping the same cascade structure of the model. The fact that the Wiener model structure is retained still allows for some physical connection to the standard models, which facilitates e.g. the interpretation of the system identification results.

Thirdly, the Wiener structure provides the system with enough nonlinear behavior, while enabling e.g. inversion of the nonlinearity, as shown in Papers V, VI, and VII. It is therefore relatively simple to use for both identification and control.

3.4.3 Other models with reduced complexity

The first publication [128] of the minimally parameterized model for the NMB, described in detail in Paper I, was followed by its extension to the DoA case [125], described in Paper II. Several other works on low complexity modeling for the effect of intravenous drugs in anesthesia has also appeared in the literature.

For the case of the NMB, the idea of using a simple model was exploited in [10, 34]. In [10] a logarithmic transformation is applied to the model output and, based on real data, a linear correlation between the effect concentration of the muscle relaxant atracurium and this transformed output variable was suggested. In [59] the model consists of a second-order linear dynamic model followed by the Hill function, of which parameters are identified using a nonlinear least squares method.

In [62], a simplified linear MISO interaction model for the effect of propofol and remifentanil in the BIS is proposed. The reasoning behind this simplification is that, in the intensive care unit (ICU), the BIS levels are inside a 40-60 window, which is the region where the interaction surface described by (3.19) is assumed to reduce to a plane [62]. The use of this linear model in a model-based controller should however be performed with some caution during e.g. the induction phase, where the BIS signals typically decrease from a value close to 100 to 30. Additional safety nets should be considered in that case. The time delay in the linear MISO relationship in [62] is estimated online by a method proposed by the same authors. The first-order plus time-delay (FOPTD) block of the FOPTD-Hill model in [143] also considers an explicit delay that is identified after the initial eight minutes of the induction phase. Nevertheless, the minimal output error-norm representation in [134] shows that, for the considered data, the model is unidentifiable along a path in the time-delay/Hill parameter space representation. The idea of using a first order transfer function followed by a time delay and the Hill function in anesthesia was also proposed in [140, 148].

Similarly to [62], the model developed in the adaptive control framework of [104] represents the interaction between propofol and remifentanil by a linear mix of effect concentrations. Again, the linearization is made around the 50% effect point. More recently, in [157] a reduced model for the hypnosis-remifentanil-induced DoA with only four parameters is proposed and its performance compared with other more complex model structures.

The fact that several research groups dedicated their efforts in reducing the model complexity aiming at model-based controllers, support the model reduction approach and subsequent choices made in this thesis.

4. Control

In this work, the focus is on control strategies based on the measurements of the control objectives of NMB and DoA, without attempting to measure or estimate disturbances. The emphasis in this chapter is therefore on output feedback control laws, and feedforward action is not treated. For a discussion on feedforward control see e.g. [26, 137, 138].

4.1 Drug delivery in anesthesia

Figure 4.1 shows a schematic view of a feedback control scheme for drug delivery in anesthesia. The control plant is the patient, the actuators are syringe pumps, and the sensors are of several kinds e.g. BIS, EMG, ECG, blood oxygenation, or temperature. The dashed lines and arrows depict indirect actions, while the solid lines and arrows depict direct actions. As an example, the anesthesiologist can only observe the tracking error, but cannot exert a direct impact to change it. The anesthesiologist's action on the error has to be indirect via changes of the setpoints of the measured effect. The variables and quantities depicted by the arrows can be vector-valued, meaning this that e.g. several sensors are placed on the patient, so that several effect measurements are performed.

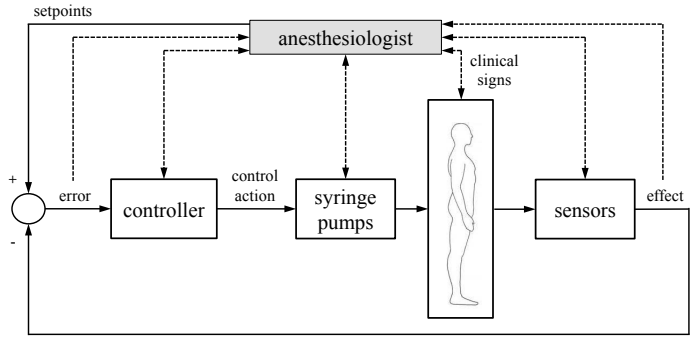


Figure 4.1. Schematic view of a feedback control scheme for drug delivery in anesthesia. The role of the anesthesiologist is that of a supervisor. The dashed lines and arrows depict indirect actions. The solid lines and arrows depict direct actions. The variables and quantities depicted by the arrows can be vector-valued.

In a general framework, automatic controllers aim at stabilization, tracking, and disturbance rejection or attenuation, while observing constraints on e.g the control input or the transient response of the closed-loop system.

The main control objectives for drug delivery in anesthesia are reference tracking and disturbance attenuation. The clinical constraints on the transient response and on the amplitude of the input signals, i.e. drug doses, should also be considered in the design. For instance, induction must be fast and over- and undershoots that may be harmful for the patient should be avoided. For the case of the NMB, overshoots as consequence of underdosing may give rise to undesired movements of the patient that the surgeon is not expecting. This may lead the surgeon to e.g. make an incision in a different place than planned. Over-dosing of muscle relaxants are not as severe. Consequences may be a delay in the recovery of the full muscular activity with the presence of residual blockade in the post-operative period [45]. As for propofol and remifentanil, overdosing may result in cardiovascular and respiratory depression. On the other hand, underdosing may lead to e.g. awareness and the recovery of the feeling of pain, which is highly undesirable [17]. In e.g. [74], avoiding overshoots was the reason to gradually rise the NMB reference at the beginning of the recovery from the initial bolus. Minimizing the undershoots in the DoA signals also led to the modification of e.g. the proportional-derivative-integral (PID) structure in [136]. Instead of reducing the integral action during induction to overcome the fact that the operating point during induction changes considerably and is far from the one used during maintenance, in [136] an additional output filter was introduced to cancel out the Hill function during induction, thereby reducing the undershoot.

A summary of design specifications in clinical anesthesia may be found in [39].

4.2 Feedback control

In this section a number of feedback control schemes are discussed. Their use in control of anesthesia is reviewed.

4.2.1 General nonlinear feedback control

Besides the main control objectives and the constraints that are present in the system, the amount of information that is available for measurement also determines which controller structures that may be used. In case all the states of the system model are measurable, or when a state observer is included in the loop, state feedback controllers [68, p. 470]

may be implemented. In other situations, when only the output is available for measurement, output feedback structures [68, p. 470] are usually chosen. State feedback control approaches include exact feedback linearization, input-output linearization and Lyapunov-based methods. These methods typically utilize the models (3.1) and (3.2).

With exact feedback linearization, the full state equation is linearized, while input-output linearization yields a linear mapping from input to output. Sometimes the linearization strategies require the solution of partial differential equations. Also, the stability of the zero dynamics should be verified to ensure closed-loop stability. In such situations adaptive implementation would create a very high computational load.

Lyapunov function-based methods guarantee stability through Lyapunov theory. The main difficulty in the design of most of these controllers is to obtain a stabilizing Lyapunov function, which is problem-specific. Sliding-mode control and back-stepping are examples of Lyapunov function-based methods that provide stabilization and tracking [68, p. 551]. However, Lyapunov function-based design can lead to conservative design of the feedback loops, with insufficient performance, see e.g. [13], if the Lyapunov function is not carefully selected.

Nonlinear control can also be performed by linearization followed by the application of methods for linear control while treating the linearization error as uncertainty. The basic limitations of the design via-linearization approaches is the fact that the controllers are guaranteed to work only in some neighborhood of a single operating point [68, p. 485]. Gain scheduling techniques overcome this limitation by changing the parameters of the controller with the operating conditions of the process [13, pp. 390-392]. This is a nonlinear feedback of a special type because the regulator is linear but its parameters are changed as a function of operating conditions in a preprogrammed way. Even though being a useful technique for reducing the effect of parameter variations, a drawback of gain scheduling is the fact that the schedule does not automatically adapt in case of uncertainties in the model. Thus, adaptation is often needed in practice anyway. Moreover, a large number of linear models and slow changes between two operating point are often required for the gain scheduling controllers to achieve a given performance [103]. This motivated the development of linear parameter-varying (LPV) models [123], system identification techniques and controllers based on LPV models that are able to deal with fast variation of the operating points and with tight performance bounds [103]. The requirement is that the nonlinear so-called scheduling parameters are measurable.

4.2.2 PID control

Proportional-integral-derivative (PID) controllers are the most widely used in industrial control systems. A PID controller calculates a tracking error e as the difference between a measured process variable and a desired setpoint. The controller steers the error towards zero by means of the proportional gain K_p, the integral gain T_i and the derivative gain T_d in the control law as follows

$$u(t) = K_p \left(e(t) + \frac{1}{T_i} \int e(s)\ ds + T_d \frac{de(t)}{dt} \right). \tag{4.1}$$

There are several established methods for tuning a PID controller [12]. A possibility is to apply a step change as input to the system and to use the open-loop response of the system to determine the control parameters, as in e.g. the Ziegler-Nichols method [160]. For the case of nonlinear systems, the nonlinear effects have to be compensated for in the design.

PID controllers have also been extensively developed and tested in anesthesia. Examples for the NMB include [74, 93], where, besides a PID with fixed gains, two other tuning strategies were tested using output information after the response from the initial bolus of atracurium. Switching between different PID controllers was also clinically tested in [94]. According to [124], the performance of these four PID controllers in fifty six clinical trials were comparable to each other, with the exception of the PID with fixed gains that presented a higher steady state tracking error.

For the case of propofol-induced hypnosis, [35] proposes an individualized tuning of a PID controller using robustness considerations. This approach delivered good results when applied to twelve virtually generated patients.

The mid-ranging MISO controller for the DoA in [135] is also based on PID and proportional controllers. The novelty in [135] is that two different filters are introduced in the loop, before the controllers. With them, the disturbance rejection bandwidth of the control system for the hypnotic depth is increased by directing the high frequency contents of the control error to the remifentanil controller.

4.2.3 Optimal control and model predictive control

In optimal control, the control design problem is formulated as an optimization problem in a systematic framework. In many real-life control problems it is nevertheless difficult to formulate the control objectives as a single objective function. Moreover, determining the optimal controller can be hard. A typical formulation of an optimal control problem

is given in e.g. [46, ch. 18]. The solution of the optimal control problem can be obtained as a state trajectory (open-loop) or as a feedback solution via the Hamilton-Jacobi-Bellman equation [8].

In industry, optimal control is often applied in terms of model predictive control (MPC). MPC has been extensively used due to its inherent robustness while at the same time ensuring that system constraints are met, see e.g. [20]. MPC is formulated as a repeated solution of a finite-horizon open-loop optimal control problem subject to system dynamics as well as input and state constraints [40].

For the case where linear models are not sufficient to describe the process dynamics adequately, nonlinear MPC (NMPC) is an alternative [40]. NMPC uses the nonlinear state space model of the system for prediction. Due to modeling errors, NMPC is more suited if a detailed first principles model is available [40]. Several existing NMPC schemes guarantee stability under full state information [61].

An open-loop optimal drug dosing control policy for ICU-sedation using a hybrid PK/PD model for propofol is suggested in [44]. The controlled variable is an integer-valued sedation score ranging from zero to six and the target for control is set in the middle of this interval. This optimal control strategy does not take into account model uncertainty and is hence challenged by the inter-patient variability.

Due to the high inter- and intra-patient variability in anesthesia, see e.g. [21, 22, 127, 143], model uncertainty should be taken into consideration in the controller design. The attempt to design feedback control to cope with a wide range of model uncertainties has lead to the development and implementation of e.g. both robust and adaptive controllers for drug delivery in anesthesia.

4.2.4 Robust control

In robust control, the model uncertainty is characterized as a perturbation of a nominal model. The nominal model may be seen as a point in a mathematical space and the perturbed models as points in a ball that contains the nominal model [68]. A robust controller assures system performance for any model inside the ball of uncertainty.

Most examples of robust control in anesthesia are based on linearization of the nonlinear model followed by a linear robust feedback controller design. The main ideas behind robust feedback controller design for linear systems are as follows.

For a controller with transfer function $K(e^{j\omega})$ to stabilize a discrete-time single-input single-output (SISO) linear system with transfer function $G(e^{j\omega})$, the open-loop frequency response of $L(e^{j\omega}) = K(e^{j\omega})G(e^{j\omega})$ must obey the stability condition

$$|L(e^{j\omega})| < 1 \text{ at } \angle L(e^{j\omega}) = -180^\circ, \tag{4.2}$$

where $|L(e^{j\omega})|$ is the gain and $\angle L(e^{j\omega})$ is the phase of the open-loop transfer function $L(e^{j\omega}) = K(e^{j\omega})G(e^{j\omega})$.

Suppose we have a SISO nominal plant $G_0(e^{j\omega})$ with a multiplicative perturbation with stable transfer function $\Delta(e^{j\omega})$, and a nominally stabilizing controller $K(e^{j\omega})$. Then the transfer function of the "true" system becomes $G(e^{j\omega}) = G_0(e^{j\omega})(1 + \Delta(e^{j\omega}))$ and the compensated open-loop transfer function is

$$\begin{aligned} K(e^{j\omega})G(e^{j\omega}) &= K(e^{j\omega})G_0(e^{j\omega}) + K(e^{j\omega})G_0(e^{j\omega})\Delta(e^{j\omega}) \Leftrightarrow \\ \Leftrightarrow \qquad L(e^{j\omega}) \qquad &= L_0(e^{j\omega}) + L_0(e^{j\omega})\Delta(e^{j\omega}). \end{aligned} \tag{4.3}$$

Since G_0, K are known and $|\Delta| < 1$, it follows from (4.3) that the "true" Nyquist plot $L(e^{j\omega})$ at any given frequency ω is contained in a region delimited by a circle centered at $L_0(j\omega)$, with radius $|L_0(e^{j\omega})\Delta(e^{j\omega})| = |L_0(e^{j\omega}) - L(e^{j\omega})|$.

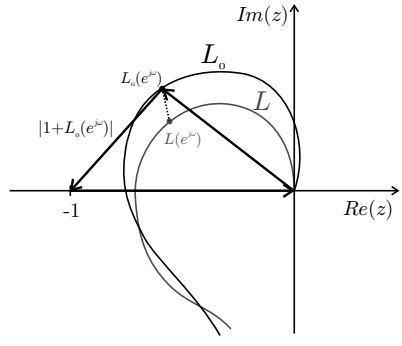


Figure 4.2. Robust stability condition (reproduced with permission from [27]).

At frequency ω, the robust stability condition for the controller $K(e^{j\omega})$, designed to stabilize the nominal model $G_0(e^{j\omega})$, to stabilize also $G(e^{j\omega})$ is

$$|L_0(e^{j\omega}) - L(e^{j\omega})| < |1 + L_0(e^{j\omega})|. \tag{4.4}$$

This is illustrated in Fig. 4.2.

The discussion about robustness is closely related with the concepts of sensitivity function $S(e^{j\omega}) = (1 + L(e^{j\omega}))^{-1}$, that maps disturbances to the output; and with the complementary sensitivity function $T(e^{j\omega}) = L(e^{j\omega})(1 + L(e^{j\omega}))^{-1}$ that maps the noise to the output.

If nominal stability holds, robust stability needs

$$|\Delta(e^{j\omega})T(e^{j\omega})| < 1, \quad \forall\omega. \tag{4.5}$$

This argument is valid for discrete- as well as continuous-time [46, pp.152-156].

In case of systems with a static nonlinearity, the work in [155] defines conditions on the controller poles so that the Popov criterion [68, pp. 275-276] cannot imply $\mathcal{L}_2$-stability, see e.g. [68, pp. 202-205], when the delays of the loop become large. In [156] an algorithm is presented that pre-computes the $\mathcal{L}_2$-stability region for a plant by a search over the uncertainty effects on the Popov inequality. The result is a robust $\mathcal{L}_2$-stable controller for cases with a static nonlinearity in the loop.

The work in [41] analyzes the robustness with respect to uncertainties of a typical controller for Wiener systems using μ-theory. The scheme is tested on a neutralization reactor in simulation showing good results.

Examples of robust feedback control strategies for the control of the NMB in anesthesia include polynomial techniques applied to pole-placement control of the linearized plant [28] and NMPC using non-parametric Gaussian process models [83]. The main drawback of the controller in [83] is the high computational load due to matrix inversions at every iteration of the MPC optimization.

For the control of hypnosis and analgesia, an extended prediction self-adaptive control - model predictive control (EPSAC-MPC) was proposed in [63]. Even though the feasibility of the controller was evaluated for twelve simulated patients, with good results, the authors of the paper acknowledge that the robustness analysis only considers the linear variability since a constant nonlinear gain was used in the controller design. The follow-up work in [100] estimates the nonlinear gain of the system from collected data during the induction of anesthesia, and uses the calculated individualized gain in the EPSAC-MPC structure afterwards. In order for this strategy to offer clinical feasibility, the effect of analgesics in the DoA still needs to be accounted for.

The robust PID control in [144] was designed for propofol administration to children and was tuned based on the frequency response of fourteen linearized models. Due to this, the controller may not be robust for cases where experimental settings change, e.g. the speed of induction or the co-administration of opioids.

4.2.5 Adaptive control

In adaptive feedback control, the uncertainty is handled via unknown parameters that the system learns online, using the input-output data. The states of the system can hence be separated into two categories [13]: the states used by ordinary feedback that change with a fast time scale, and the parameters, here seen as states, that change with a much slower time scale.

In an adaptive control setting, there is the choice of what parameters to estimate. In direct algorithms, the controller parameters are updated

directly. If the controller parameters are obtained via design procedures, the algorithms are called indirect. This difference is made clear in the discussion of the two structures of adaptive controllers that follows.

The model reference adaptive system (MRAS), of which a block diagram is shown in Fig. 4.3, is a direct algorithm. The system consists of two loops: the inner loop provides the ordinary feedback control, and the outer loop adjusts the parameters of the regulator in the inner loop. The desired performance of the MRAS is expressed in terms of a reference model, which gives the desired response to a command signal [13, p. 105].

The approaches to analyze and design MRAS include the gradient approach, Lyapunov functions and passivity theory [13]. The assumption that the parameters vary slower than the other variables in the systems is crucial for the computation of the sensitivity derivatives that are needed in the adaptation mechanism of e.g. the gradient approach. Due to the fact that the gradient approach does not necessarily result in closed-loop stability, modifications to this initial idea were proposed using Lyapunov stability theorem and passivity theory [68].

The self-tuning regulators (STR) are indirect algorithms. A block diagram of a STR is shown in Fig. 4.4. The estimation algorithm updates the process parameters and the regulator parameters are obtained from the solution to a design problem. The STR scheme is flexible with respect to the choice of the underlying design and estimation methods.

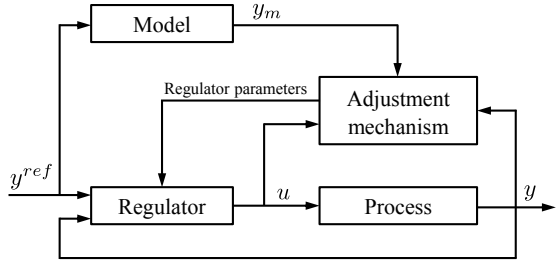


Figure 4.3. Block diagram of a model-reference adaptive system (MRAS) [13]: y is the process output; u is the process input; y^{ref} is the reference signal, and y_m is the reference model output.

In the MRAS and the STR, the controller parameters or the process parameters that are estimated in real time are used in the controller as if they were equal to the true ones. This means that the uncertainties of the estimates are not explicitly taken into account in the design. This is sometimes denoted the certainty equivalence principle.

Several strategies with parameter adaptation have been proposed for both the NMB and the DoA control.

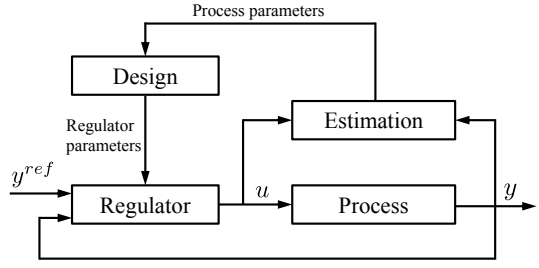


Figure 4.4. Block diagram of a self-tuning regulator (STR) [13]: y is the process output; u is the process input, and y^{ref} is the reference signal.

The adaptive generalized predictive control (aGPC) in [129] recursively identifies the parameters of a third-order discrete-time ARX-model to model the effect of mivacurium in the NMB. The model estimates are then used in a standard generalized predictive control (GPC) formulation.

The Lyapunov function-based direct adaptive controller for non-negative compartmental systems in [104] presents a general framework for the regulation of multiple drug effects. Simulations were presented for the case of propofol-remifentanil-induced DoA, where remifentanil enters as an accessible disturbance. Since the algorithm considers that the effect concentration of both drugs and the compartmental rate constants are known, which is not the case in real practice, some extensions still have to be made before applying this idea to practical cases.

4.2.6 Intelligent and rule-based feedback control

Intelligent control systems are typically able to emulate the human behavior, learn from past experiences, integrate sensor information and/or identify changes that threaten the system behavior, e.g. failures, and react appropriately. Fuzzy systems, neural networks, machine learning, multi-sensor integration, and failure diagnosis are hence research areas that are closely related and important to intelligent control.

Examples of fuzzy controllers for the DoA are found in [64, 85]. In [54], a neuroadaptive output feedback controller for propofol is proposed and evaluated both in simulation and in clinical trials. A reinforcement learning controller based on Markov decision processes is designed for optimal control of propofol-induced hypnosis in [98]. A review of intelligent modeling and control in anesthesia is available in [75].

The main drawback of the intelligent controllers is the difficulty in analyzing the system closed-loop behavior due to the high complexity of the design.

Examples for heuristic rule-based control strategies include e.g. [56, 78, 139]. The controllers in [78, 139] rely on a TCI system. In [78], the calculations of the target effect concentration are based on PID controllers with gains determined empirically when certain conditions in the rate of change of the drugs and BIS signal hold. In [139], data from open-loop induction are used to identify the parameters in the Hill function. After induction, small errors are compensated for by a proportional controller. Large errors lead to a shift in the Hill function along the effect concentration axis. Even though these heuristic methods performed adequately in the first trials, due to the lack of background theory supporting their development, an extended feasibility, robustness and stability assessment should be performed before these controllers become accepted in the daily clinical use.

A list of clinical and simulation studies of EEG-guided closed-loop control using propofol or remifentanil between 1989 and 2013 may be found in [134, Appendix C]. References to other advanced control strategies for the DoA may be found in [158].

4.3 Nonlinear feedback control of Wiener systems

4.3.1 General controller structures

Feedback controllers for Wiener systems can be designed with linear methods after a nonlinear step where the inverse of the nonlinearity is applied to the reference signal and to the measured output. This methodology is discussed in [13]. Figure 4.5 shows a block diagram of the linearizing controller.

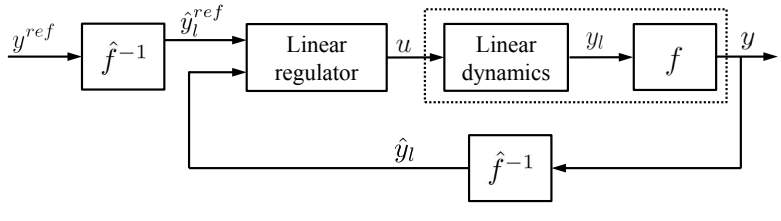


Figure 4.5. Linearizing controller: u is the input signal; y_l is the output from the linear block of the Wiener model; y is the output signal; f is the nonlinear function of the Wiener model; y^{ref} is the output reference, and $\hat{y}_l^{ref}$ is the linearized output reference. The hat in $\hat{y}_l$ and in $\hat{f}^{-1}$ denotes the estimates.

The parsimony of the models proposed in this thesis has made it possible to develop system identification algorithms to obtain online estimates of the parameters of a Wiener model. Hence, by inverting the static nonlinearity in the Wiener model using the current estimate of the parameter

in the nonlinearity, the system is approximately linearized and the time-varying changes in the loop gain of the system are compensated for. This possibility motivated the use of the linearizing controller in Fig. 4.5 in this work.

Other control strategies for Wiener systems exist and some examples follow. In [29] a nonlinear model predictive controller based on a Wiener model with a piecewise linear gain is presented. This approach retains all the properties of the classical linear MPC and keeps the computational requirements low using a canonical structure of the nonlinear gain. A MRAS for cases where the output of the linear block of the Wiener model is not available is proposed in [106]. Other examples of adaptive controllers include e.g. the linearizing feedforward-feedback control of [67], and the Wiener model predictive control (WMPC) of [102]. Robust internal model control (IMC) of stable Wiener systems with unstable zero dynamics, unmeasured states, disturbances and measurement noise is also proposed in [69].

4.3.2 Controllers using minimally parameterized models

Since the first publications [125, 128] of the minimally parameterized models described in detail in Papers I and II, several control strategies using those models have been proposed and some undergo clinical tests at the moment.

In [142], a switching strategy for the control of the NMB is presented. The switching setup uses the models in the database generated in [114] for atracurium and the models identified in [126] for rocuronium.

In [9], a control scheme based on a positive control law for feedback stabilization of compartmental systems was modified to tackle model uncertainties. These model uncertainties occur since the online identification of the NMB model parameters is only performed during the manual induction phase and stops when the controller is working.

In [101], a multiple-input single-output (MISO) positive control strategy for the DoA is developed and tested in simulation using the models identified in [92].

4.4 Experimental setup: Galeno platform

The Galeno platform [4, 107] constitutes a follow-up version of the Hipocrates software package [2, 94]. It is a computer application developed for research and development of methods for automation in anesthesia and it is available at Universidade do Porto, Portugal. The current version of the platform enables e.g. closed-loop control of NMB, closed-loop con-

trol of DoA-hypnosis and open-loop control of analgesia, with minimal intervention of the anesthesiologist.

The Galeno platform comprises:

- sensors/monitoring devices, e.g. the NMB and BIS sensors in the anesthesia workstation that are connected to the patient;
- actuators/syringe pumps that intravenously deliver the muscle relaxants, hypnotics and analgesics to the patient under anesthesia;
- laptop with the Galeno software [4, 107] implemented, and connected via the serial ports to the syringe pumps and to the anesthesia workstation.

Figure 4.6 shows an overview of components of the platform Galeno, while in use in the surgery room.

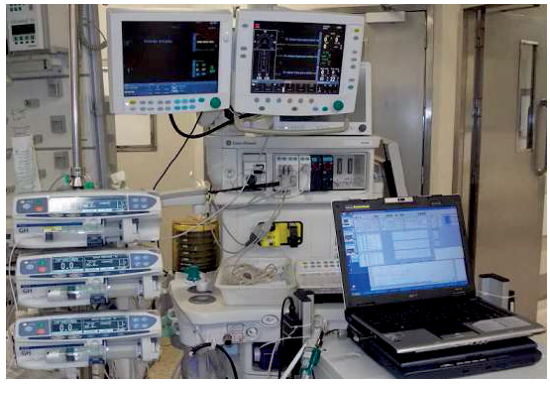


Figure 4.6. Overview of the components of the platform Galeno [4, 107].

The platform architecture is structured in two application-components, the Galeno-data acquisition drivers (GDAD) and the Galeno-monitoring and control of anesthesia (GMCA). The GDAD were developed using the programming language C# and are used only in real-time mode, with the main purpose of implementing an abstraction of the communication between the GMCA and the different syringe pumps and monitoring devices. The GMCA application was developed using Matlab (version 7.9.0.529, R2009b, win32) and may be used in real-time mode or in off-line mode for simulation and train/test experiments. The main motivation to use Matlab to implement GMCA is that it allows fast software prototyping and it facilitates the access to mathematical functions and methods that are necessary to implement the algorithms for identification and control.

4.5 Patient safety

The need to account for patient safety is one of the reasons why no closed-loop control system has passed the prototyping barrier and became widely accepted and used in the daily clinical practice. As an example, [86] describes the regulatory challenges that a closed-loop anesthesia delivery product has to overcome in the United States of America before being successfully introduced into the market and incorporated into general practice. The likelihood of approval is likely to increase with demonstration of a clinically significant safety benefit [86]. A reduction of the incidence of awareness or in the incidence of overdose-related post-operative complications as compared to standard clinical practice are examples of benefits that are related with robustness and stability of the closed-loop control solutions. Therefore, it is important that control experts are at the heart of the development of those systems to ensure that they are based on solid control theory with the theoretical properties analyzed in detail. Ideally these analyses provide safety margins that should be automatically maintained by the system. This also provides a need for fault detection systems in the closed-loop anesthesia setting. The system should hence request for the anesthesiologist's intervention or for a more careful supervisory action during the period where the theoretical requirements for e.g. robustness or stability are not met.

4.5.1 Nonlinear behavior of closed-loop systems

One of the "essentially nonlinear phenomena" of dynamic systems are sustained oscillations, usually termed as limit cycles [68]. For a linear system to oscillate, it must have a pair of eigenvalues on the imaginary axis. The amplitude of such oscillations depend on the initial conditions. However, nonlinear systems may go into an oscillation with fixed amplitude and frequency, irrespective of the initial state [68]. Oscillatory behavior in nonlinear systems can arise due to e.g. bifurcations [76]. A bifurcation is a change in the equilibrium points or periodic orbits, or in their stability properties, as one or more parameter in the system is altered [68].

Consider the general case of a nonlinear system defined by $\dot{x}(t) = f(x, \mu)$, being $x \in \mathbf{R}^n$ the state vector, $\mu \in \mathbf{R}^m$ the bifurcation parameter, and f a smooth nonlinear function that maps $\mathbf{R}^n \times \mathbf{R}^m$ into $\mathbf{R}^n$. If a pair of complex conjugated eigenvalues of the Jacobian matrix of f calculated at the system equilibrium point x_0, simultaneously crosses the imaginary axis due to a change in the bifurcation parameters μ [50, pp. 151-152], a Hopf bifurcation (or Andronov-Hopf or Poincaré-Andronov-Hopf bifurcation) arises, leading to the emergence of a limit cycle. This kind of oscillatory dynamics typically arises in systems with

negative feedback when the loop gain and/or the delay in the feedback loop becomes significant.

The first scenario that can happen is when, via a change of μ, a stable equilibrium x_0 becomes unstable. In this case, the limit cycle that arises surrounding the unstable equilibrium in the phase plane is stable, and the bifurcation is called a supercritical Hopf bifurcation. The limit cycle has zero amplitude at the parameters of the Andronov-Hopf bifurcation μ_0 and at the equilibrium x_0. The amplitude grows roughly with the square root of the distance to the bifurcation point as the parameters move further into the limit-cycle regime [76]. Supercritical bifurcations are sometimes called soft (or safe) because when the equilibrium disappears due to small perturbations, the system will experience steady-state oscillations with a small amplitude.

The second scenario that can happen is when, via a change of μ, an unstable equilibrium becomes stable. In this case, the limit cycle that arises surrounding the stable equilibrium in the phase plane is unstable, and the bifurcation is called a subcritical Hopf bifurcation. The subcritical Hopf bifurcations are hard (or dangerous) because small perturbations of a nominal stable equilibrium could force trajectories to move away from the equilibrium.

In order to give an illustrative example, assume that α is the bifurcation parameter and x_1 and x_2 are two states of the state space representation of the system modeled by $\dot{x} = f(x, \alpha)$, with $x = [x_1 \quad x_2]^T$ as the state vector.

In Fig. 4.7a, the equilibrium (i.e. the origin) is a stable focus if $\alpha < 0$. The bifurcation condition is $\alpha = 0$. For $\alpha > 0$ the equilibrium becomes an unstable focus, surrounded by a closed stable orbit (limit cycle). All orbits starting outside or inside the cycle except at the origin tend to the cycle as $t \to \infty$.

For the case of subcritical bifurcations shown in Fig. 4.7b, the system presents an unstable limit cycle that disappears when the bifurcation parameter α crosses zero from negative to positive values.

Examples of the presence of Hopf bifurcations in biological and biomedical systems include e.g. autoimmune disease processes [76], non-basal testosterone regulation [159], and biochemical networks [147]. The work in [52] shows that the equilibria of the central nervous system model exhibit multistability and bifurcations that depend on the time constants of the system. It is also suggested that in general anesthesia these time constants may be related to the concentration of anesthetics.

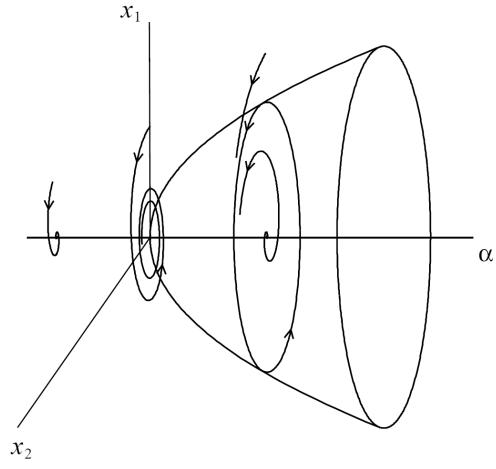
4.5.2 Bifurcation analysis in anesthesia

The effect of drugs in anesthesia is an intrinsically nonlinear process. The incorporation of controllers in the loop adds further nonlinearities and rises the question on whether nonlinear phenomena such as sustained oscillations may appear. In fact, there is clinical evidence [7, 54, 64, 91] of oscillatory behaviors in closed-loop drug delivery systems in the literature.

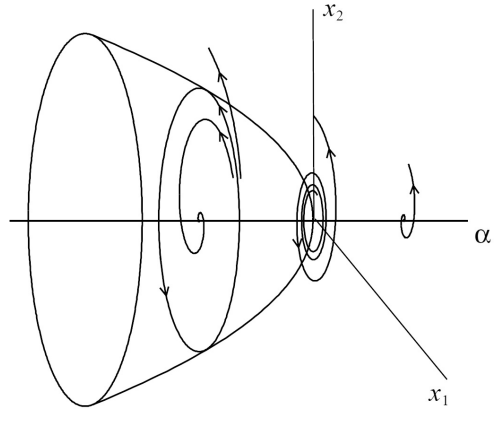
In what the NMB is concerned, when underdosed, the patients' muscles might contract in response to the surgical stimulation, which might constrain the surgeons' actions or even cause severe harm at the moment of the unexpected contraction. If overdosed, saturations might occur, which bring potential delays in the recovery and a risk of residual blockade in the post anesthetic period [45].

Related with the DoA, almost all hypnotics and analgesics are myocardial depressants, meaning that they decrease the strength of the contraction of the heart and lower cardiac output. Hence, a consequence of overdose includes a slow down of the transfer of blood from the central compartments to the peripheral compartments of muscle and fat. This delay can lead to overdosing that, at the very least, can delay recovery from anesthesia and, in the worst case, result in respiratory and cardiovascular collapse. On the other hand, underdosing can cause psychological trauma from awareness and pain during surgery [17].

These negative consequences of under- and overdosing of anesthetics justify the development of the work in Paper VIII. The case of PID-controlled NMB is treated. The results show that the minimally parameterized parsimonious (MPP) model for the NMB is able to capture the same intrinsic nonlinear dynamics of the system, like limit cycles and sustained oscillations, as the standard physiologically-based PK/PD model. This is another indicator that the proposed MPP models should be used for the design of controllers for drug delivery in anesthesia.



(a) Supercritical Hopf bifurcation.



(b) Subcritical Hopf bifurcation.

Figure 4.7. Hopf bifurcations in the phase-parameter space (reproduced with permission from [73, pp. 88-89]).

Summary in Swedish - Sammanfattning

Då en person undergår kirurgi är narkos nödvändigt. Vilken typ av bedövningsmedel som ges till patienten beror på dennes medicinska tillstånd samt vilken typ av kirurgi som ska utföras. De olika typerna inkluderar lokal, regional och allmän bedövning. Den här avhandlingen behandlar allmän bedövning. Vid allmän bedövning ska patienten vara helt medvetslös, och efteråt inte kunna minnas vad som hände under operationen. Patienten ska inte heller känna någon smärta vid ingreppet och vara helt avslappnad i alla muskler så att kirurgen lätt ska kunna komma åt de inre organen. Ett sådant tillstånd skapas och bibehålls genom en noga avvägd dosering av bedövningsmedel. I nuvarande klinisk praktik, är anestesiologen den som manuellt justerar den mängd bedövningsmedel som levereras till patienten. Beroende på patients reaktion och förändringar i de variabler som övervakas, så ökas eller minskas tillförseln av bedövningsmedel. På grund av den stora variationen mellan olika patienter och osäkerheten i de mätta variablerna, kan detta vara en svår uppgift, vilket kan leda till under- eller över-dosering. En underdos kan leda till att patienten blir medveten eller gör oönskade rörelser. En överdos kan leda till hjärtproblem och en längre återhämtningstid efter kirurgin. Den potentiella förbättringen som automatisering kan tillföra till allmän bedövning är därför stor. Precis som inom andra medicinska discipliner kan regulatorer behandla alla tillgängliga mätningar från patienten i realtid och beräkna den grad av styrning som ska utföras så att de önskade värdena för de involverade kvantiteterna nås och bibehålls. I fallet med dosering av bedövningsmedel är styringreppet den mängd bedövningsmedel som ges till patienten och mätningarna är indikatorer som reflekterar hjärn- och muskelaktivitet. För att kunna göra en god bedömning av hur mycket bedövningsmedel som ska ges till patienten vid en given tidpunkt behövs matematiska modeller som förklarar fördelningen och effekten av bedövningsmedel i kroppen.

I den första delen av avhandlingen föreslås modeller av låg ordning (och med få parametrar) för att beskriva effekterna av bedövningsmedel. Tanken är att modellerna i realtid ska kunna anpassas till patienten som genomgår kirurgin. Detta görs genom att studera mängden bedövningsmedel som givits och responsen hos patienten. I den andra delen av avhandlingen utvecklas regulatorer för problemet. Regulatorerna baseras på de modeller som skattas i realtid och beräknar, utan hjälp av anestesiologen, den dos av bedövningsmedel som ska ges till patienten. Regleral-

goritmen avläser data från klinska monitorer, beräknar mängden bedövningsmedel, och skickar dessa värden till injektionspumpar kopplade till patienten. Det finns således en sluten krets som fungerar automatiskt. Anesteologen har då en övervakande roll, ifall sensorer inte fungerar eller störningarna är så stora att de inte kan hanteras av regleralgoritmen.

I avhandlingen har de framtagna regulatorerna provats både i simulering och i kliniska försök. Resultaten visar en god följning av börvärdena för både muskelavslappning och nedsövning. Den mängd bedövningsmedel som beräknades av regulatorerna och levererades till patienterna följer de riktlinjer som finns och inga tecken på över- eller underdosering observerades. Både ingenjörerna och den medicinska expertisen som deltog i de kliniska försöken godkände resultaten.

En matematisk studie av återkopplingarna visar att både standardmodellerna och de nyligen förslagna modellerna kan trigga ett komplicerat olinjärt beteende för det slutna systemet. På grund av de höga kraven för patientsäkerhet vid automatisk reglering, har villkor som garanterar säker reglering av muskelavslappningen också tagits fram. Riktlinjer för design av regulatorer som inte arbetar i de kritiska regionerna, där dålig reglerprestanda och oscillationer kan uppstå, anges i avhandlingen.

Summary in Portuguese - Sumário

Qualquer intervenção cirúrgica envolve anestesia. Dependendo do protocolo cirúrgico em questão e da condição geral do paciente, o tipo de anestesia pode ser local, regional ou geral. Esta tese aborda o caso de anestesia geral. Durante um episódio de anestesia geral o paciente deve estar inconsciente, não deve sentir dor e não deve ter tónus muscular de modo a que os cirurgiões possam aceder facilmente aos órgãos internos do paciente. Para além disso, no período pós-operatório, o paciente não se deve lembrar do que aconteceu durante a cirurgia. Estas condições são induzidas e mantidas devido à administração de fármacos anestésicos. Na práctica clínica actual, o anestesista ajusta manualmente a dose de fármacos a serem administrados ao paciente. Tendo em consideração os sinais do paciente e a alteração das variáveis fisiológicas que são monitorizadas, o anestesista aumenta ou diminui a dose de fármacos necessária. Devido à grande variabilidade entre pacientes e ao ruído presente nas variáveis monitorizadas, esta tarefa pode ser exigente, podendo resultar numa indesejada sub- ou sobre-dosagem de fármacos. Se, por um lado, uma sub-dosagem de hipnóticos e analgésicos pode levar à presença de consciência ou movimentos indesejados por parte do paciente; por outro, uma sobre-dosagem pode originar complicações cardio-vasculares e uma recuperação prolongada no período pós-operatório. Consequentemente, o potencial do uso de automação num cenário de anestesia geral é elevado. À semelhança de outras áreas da medicina, o objetivo é que controladores automáticos para anestesia recebam e processem todas as medições disponíveis do paciente em tempo real e calculem a ação a ser tomada de modo que os valores desejados para as medições envolvidas sejam atingidos. No caso da administração de fármacos em anestesia, as ações são a dose de fármacos a ser administradas aos pacientes, e as medições são índices que refletem a atividade cerebral e muscular. No sentido de tomar uma boa decisão sobre que dose administrar em cada instante de tempo, são necessários modelos matemáticos que expliquem a distribuição e o efeito de anestésicos no corpo humano.

Na primeira parte desta tese são apresentados modelos com poucos parâmetros que descrevem o efeito de relaxantes neuromusculares, hipnóticos e analgésicos. A ideia é que, em tempo real, estes modelos possam ser adaptados a cada paciente específico sob anestesia. Esta adaptação é feita considerando a dose de anestésicos administrada até ao momento e a resposta do paciente a esses anestésicos. Na segunda parte da tese

são apresentados os controladores automáticos desenvolvidos. Os controladores usam os modelos cujos parâmetros são estimados em tempo-real e, sem influência do anestesista, calculam a dose de fármaco a ser administrada ao paciente. Os algoritmos de controlo recebem os dados dos monitores clínicos, calculam a quantidade de anestésicos, e enviam esses valores para as seringas ligadas ao paciente. Este processo constitui uma malha-fechada que trabalha automaticamente. O anestesista tem, naturalmente, um papel de supervisão importante, nomeadamente devido à presença de falhas dos sensores ou elevadas perturbações no sistema com os quais a malha-fechada de controlo não é capaz de lidar. Nesta tese, os controladores desenvolvidos são testados em simulação e em ambiente clínico. Os resultados mostram um bom seguimento da referência desejada para o relaxamento neuromuscular e profundidade de anestesia. As doses de fármacos calculadas pelos controladores e administradas aos pacientes estão de acordo com as recomendações dos laboratórios e com a prática clínica. Para além disto, nos testes efetuados não houve sinais da presença de sobre ou sub-dosagem. Tanto os engenheiros e matemáticos como os médicos que participaram nos testes clínicos manifestaram-se satisfeitos com os resultados.

Para além do acima mencionado, foi desenvolvido um estudo matemático do sistema em malha fechada que mostra que, tanto os modelos standard para o efeito de fármacos num paciente sujeito a anestesia geral, como os modelos reduzidos propostos nesta tese, podem levar ao aparecimento de padrões de funcionamento intrinsecamente não lineares. Devido à necessidade de garantir segurança no funcionamento de qualquer controlador em ambiente clínico, foram também determinadas condições que garantem o não aparecimento de padrões de funcionamento indesejáveis de controladores para relaxantes musculares. São também delineadas estratégias para desenho de controladores que não entram em zonas de oscilações indesejáveis das variáveis fisiológicas em questão, garantindo assim um funcionamento seguro do sistema de controlo em malha-fechada.

Acknowledgments

A PhD program is a journey that only makes sense when done jointly with intelligent persons, and I am thankful for having met them.

First of all I would like to acknowledge the support and guidance of my supervisors Associate Prof. Teresa Mendonça, Prof. Alexander Medvedev and Adjunct Prof. Torbjörn Wigren. Thank you, Teresa, for having shown me that anesthesia through a computer and a mathematician's eye can be fun, and for having provided me with so many opportunities to grow scientifically. Thank you, Alexander, for all the inspiring ideas during the last leg of this journey. Unveiling the mysteries of a biomedical system with your supervision was actually not that nonlinear. Thank you, Torbjörn, for having believed in me from the very beginning, when not even a PhD was at sight, for being available unconditionally, and for being such a role-model during these five years.

I believe that part of the success of this journey relies on the fact that I was always so welcomed by the Syscon team and the administrative staff of the IT department whenever I moved back to Uppsala. Thank you all. A special thanks to Prof. Håkan Lanshammar for all the effort and time put in establishing the individual agreement between Uppsala University and Universidade do Porto. Also, thank you, Olov and Per for the translation to Swedish of the summary of this thesis. Equivalently, for having commented the Portuguese summary, "obrigada Vinicius e família maravilha", and for having proof-read the abstract, thank you, Laurent.

All my co-authors, the members of the IDeA/Galeno team, and the anesthesia staff from Hospital de Santo António, Centro Hospitalar do Porto and from Unidade Local de Saúde de Matosinhos should be acknowledged for the ideas, discussions and feedback.

The financial support from Fundação para a Ciência e a Tecnologia via de individual grant SFRH/BD/60973/2009, and the European Research Council via the Advanced Grant 247035 are gratefully acknowledged. Also, for the travel grants that I received, a sincere acknowledgment to Fundação Luso-Americana para o Desenvolvimento, Fundação Calouste Gulbenkian, Bernt Järmark's Foundation for Scientific Research, Uppsala University for the Liljewalch travel scholarship, and the student travel awards sponsors of the American Control Conferences in the years 2010 and 2014. To the friends that I made and with whom I had the pleasure to share my time during conferences, a special thanks.

A sincere thanks to FH-Prof. DI Dr. Gerhard Jöchtl and FH-Prof Univ.- Doz. Mag. Dr. Steffan Weggenkittl from the Fachhochschule Salzburg for having made my ERASMUS-during-PhD possible.

To the friends that I have made in Uppsala, thank you for the uncountable fikas and afternoons strolling around. My dearest Camille and Chris, it was quite a coincidence that we became friends but sometimes the randomness of things is surprisingly awesome.

To the ones that brought a bit of Portuguese taste to my stay from the very beginning of my last year in Uppsala, thank you André, Xana, Daniel and Leonor.

To my beautiful girl-friends, Barradas, Nery, Mafalda and Becas, it is amazing how much positive energy I retrieve from email lines and phone calls with you. Thank you for always having time to listen to my "problems" and for the good advices and insights.

Last but not least, I should apologize to all that contributed to this journey and that I, by no deliberate intention, forgot to mention. Your contribution was definitely welcomed. Thank you.

"Aos meus pais, Catarina e Reini, obrigada por incondicionalmente me mostrarem o quão grande é o lugarzinho especial que ocupo no vosso coração."

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