Feedback Control of Hypnosis and Analgesia in Humans

A dissertation submitted to the Swiss Federal Institute of Technology (ETH) Zürich for the degree of Doctor of Technical Sciences

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Foreword

The purpose of this section is threefold. First, I would like to address some issues that a Ph.D. candidate must face towards obtaining the final degree, proposing a tentative solution to the avoidable difficulties coupled with a Ph.D. program. Second, I would like to mention how this thesis was structured and how should the reader go through it. Third, I would like to acknowledge the people who significantly contributed to the success of this thesis.

An easier start-up

I conceived these few lines while training for marathons during the first two years of my stay at the Automatic Control Laboratory. I decided to do so at that time because looking at the former graduate students’ smile when they finally obtained their Ph.D. degree made me think that I would have been too excited towards the end to be able to draw rationale conclusions about such an important period of my life.

The path towards obtaining a Ph.D. degree is not always straight. Even though this is known to all the researchers who successfully completed a Ph.D. program, few of them decided to share their experiences for the benefit of future Ph.D. candidates. I will try to do so here by giving my personal answer to two crucial questions, which may be of interest also for senior researchers supervising Ph.D. candidates.

What are the avoidable and unavoidable difficulties encountered during a Ph.D. program? How can the avoidable difficulties be removed?
Let us start by setting obvious premises: the goal of every Ph.D. candidate is to discover something new and to communicate it to the scientific community through scientific publications in high quality journals. Hard challenges convey big troubles, some of which may be easily avoided with a new approach to the management of the human resources. Not withstand¬ing the fact that - for the limited experience that I have from visiting other research labs - the institute I was working in provides excellent infrastructure to perform outstanding research. And this is the reason why I speak up these words: because such an excellent background must be exploited at best to get the highest return to the strong investment which was visibly put into building such an infrastructure.

A particularly delicate period of the Ph.D. program is represented by the first months where a specific research goal is not yet outlined and the ignorance in the field is often total, presuming that one has not been previously engaged in the same research direction. Other apparently less relevant uncertainties may disorient. They are associated to questions like which type of journal should I target for my publications, which conferences and lectures should I attend, which institutions may be worth a visit during my Ph.D. program. These latter, which seem to be more burocratical details than anything else, may interact in a dangerously synergistic way with real research problems and ultimately increase confusion. As a result, the first real research contributions are delayed in time. Very often, one is reaching the end of the Ph.D. program with a very detailed map of new research directions which may be worth to be pursued. At that time though, often the last round bell rings and the time to move from intentions to actions lacks.

One feasible solution to the inevitable bewilderness of the initial period may be a mentor for the start-up in the research work, a Virgilio guiding the graduate student through the hell of the first months. In my personal view, this guide must not be the Ph.D. advisor, whose main duties such as reviewing, teaching, traveling and managing the research institute do not allow her/him physically to be constantly after the Ph.D. candidate. Moreover, etymologically speaking, her or his role is more to give ‘advice’ than to lead the way.

The person I am pointing at could be anybody like a senior or post-doc researcher or even a graduate student approaching the end of her/his Ph.D.
program who has been working in a similar field. Those persons know what to do, know how to do it but they lack time and manpower. The mutual interest in a collaboration between an experienced researcher and a ‘fresh’ Ph.D. student is quickly defined. The senior researcher may enjoy seeing the development of her/his idea without losing contact with other activities. The young researcher enjoys the experience of the senior, learns the way through daily technical difficulties, acquires discerning capabilities about the directions which are worth an investigation and the ones which are not, experiences the importance of the communication of scientific results. The concrete goal of such a tight teamwork may be anything which can be considered as a ‘research output’ such as a journal or conference paper and/or a postgraduate thesis. Needless to say, the success of such a collaboration strongly depends on the characteristics of the individuals. Particularly important keys to success beyond the technical skills may be the natural disposition to teamwork, the will to share knowledge and the commitment to solve conflicts in view of the big picture. At the end of the mentorship program, a cross evaluation of the respective partner may also be beneficial for both: the young researcher would receive important feedback about the strengths she/he may want to exploit further and the lacks which need to be compensated. The senior researcher may benefit from the feedback about her/his leadership and management capabilities, which may help her/him further in the career.

I firmly believe that the interaction among people potentiates the strengths of the single individuals. It is also true, however, that the Ph.D. is ultimately a success of the candidate herself/himself and nobody else. Becoming aware of this and moving consequently is a major achievement during the graduate program.

To give answers to the questions stated initially, the initial lack of orientation of the Ph.D. program is an avoidable difficulty. Assigning a senior researcher as a mentor for the Ph.D. candidate may be a solution to the problem. Defining a research output such as a common publication as the goal of the relationship enables the Ph.D. candidate to communicate research results during a period where normally no output is produced. Further, it allows the mentor to test her/his leadership capabilities. An example of organizations where mentorship programs are successfully used are consulting companies, for the simple reason that the richest skills of a consultant come from their experience. And one of the most fruitful of those skills is
the intuition for opportunities. A recently hired consultant not only lacks experience, but could create damage for the company trying to establish one. Further, it would certainly take a period of time the company cannot afford to pay. The reasons which motivate the adoption of a mentorship program in consulting companies may hold also for the academic environment. Mentorship programs may be an easier start-up for Ph.D. candidates.

For the reader

Chapters 1, 2, 3 and 4 of the present thesis are partially modified stand-alone publications. A foreword section is given at the beginning of each chapter to inform the reader about where she/he can find the original publication and how does the present chapter relate to others in the big picture of the thesis. After having summarized the main achievements of the thesis, chapter 5 provides an outlook for future research directions.

Acknowledgments

This work would not have been possible without the help and the support of many people. Among my colleagues at IfA, I am particularly thankful to Christian Frei, Marco Derighetti, Prof. Adolf Hermann Glattfelder and Konrad Stadler who have been precious partners during several research discussions. To Marco Sanvido, whose wide expertise in computer science often prevented the real-time platform from collapsing. Finally, a special acknowledgment to Gianni, Eleonora, Francesco, Alberto, Domenico and Milos with whom I lived many critical and exciting situations and to Fabio, with whom I shared the office with the most gorgeous sight of town.

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Abstract

The main contribution of this thesis is the design and the application of two novel feedback control systems to the practice of general anesthesia. Both improve the patient care during and after general surgery. The first aims at regulating the patient’s degree of unconsciousness by continuous administration of volatile hypnotics. The second aims at regulating the patient’s analgesic state by means of continuous opiates infusion. Another contribution of the thesis consists in the development of a new modeling framework to quantify anesthetic drug synergies.

In the introduction we thoroughly analyze all the potential benefits of automation in anesthesia. As an example, two control strategies are presented for the particular cases of Mean Arterial Pressure (MAP) and Bispectral Index (BIS) regulation with isoflurane. Further, we describe the real-time platform which allows us to apply closed-loop control in the operating room. In particular, we discuss the mandatory safety measures that cope with the clinical safety standards and the software architecture.

Chapter 2 describes the model-based closed-loop system which delivers isoflurane to guarantee unconsciousness as assessed through Bispectral Index (BIS). This has been the first model-based closed-loop controller of hypnosis with volatile agents ever tested on humans. The conception of this controller was triggered by the increasing use of BIS monitors in the clinical practice. BIS monitors were the first clinical devices to receive Food and Drug Administration clearance as monitors for unconsciousness. BIS monitors compensate for the lack of a reliable sensor for awareness, a deficiency since the first successful surgical intervention with anesthesia in 1846.
The results of the clinical validation of the controller on humans are presented. The patent for the control strategy to regulate BIS is pending in both the European Community and the United States of America.

Chapter 3 describes a model-based closed-loop system for the intraoperative administration of analgesics. This has been the first model-based closed-loop control strategy to regulate analgesia ever tested on humans. The ideal input for the control system is still missing, since pain cannot be assessed while the patient is unconscious. Therefore we developed a closed-loop controller which has two goals. On one hand, it maintains the patient’s hemodynamic stability assessed through MAP, a possible candidate indicator for the analgesic state. On the other hand it tracks predicted analgesic concentrations in the plasma, allowing anesthesiologists to titrate opiate infusion on the basis of clinical signs of inadequate analgesia.

In chapter 4 the problem of anesthetic drug interaction is addressed. Precisely, we present a modeling framework which is suitable to quantify and test anesthetic drug synergies. Even though several synergy models were already presented in other medical fields such as cancer therapy, they are not adequate in anesthesia. The main assumption which is violated for anesthetics drugs is that all the compounds in the mixture investigated must have an effect on the considered clinical endpoint if given alone. The novel modeling framework is able to describe mixtures of two and three anesthetic drugs. Further, single drug parameters can be embedded in the model equation without the need to be re-estimated.

In chapter 5 we summarize the main achievements of the thesis and outline future research directions.
Zusammenfassung


Im Kapitel 1 analysieren wir die möglichen Vorteile der Automatisierungstechnik in der Anästhesie. Als Beispiel nehmen wir die Regelstrategien, die den Mittleren Arteriellen Druck (MAP) und den Bispektrale Index (BIS) mit Isofluran regeln. Dann beschreiben wir die technischen Lösungen, welche die notwendige Sicherheit unserer Geräte garantieren und die Architektur unserer Software Applikationen, mit welchen wir die Regler in der Klinik anwenden können.

Im Kapitel 2 beschreiben wir die erste je am Menschen getestete modellbasierte Reglerstruktur, welche eine gewünschte Hypnosetiefe erreichen und halten kann. Die Hypnosetiefe wird durch die Messung des Bispektral-Index abgeschätzt und durch die reglerkontrollierte Verabreichung des flüchtigen Anästhetikums Isofluran erreicht. Die zunehmende Verbreitung der BIS Monitore im klinischen Bereich hat den Anstoss zur Entwicklung eines solchen Reglers gegeben. Die BIS Monitore sind die ersten Geräte für die Messung der Hypnosetiefe, die von der ‘Food and Drug Administration (FDA)’ zur Verwendung der Klinik zugelassen wurden.

Für die Regelungsstrategie wurde ein Patent bei der Europäischen Union
angemeldet.


Im Kapitel 5 fassen wir die Kernpunkte dieser Dissertation zusammen und stellen mögliche Richtungen für die zukünftige Forschung vor.
Prefazione

Questa tesi descrive due nuovi paradigmi di controllo ad anello chiuso applicati nel campo dell’anestesia generale. Il primo controllore regola il grado di ipnosi del paziente mediante la somministrazione continua di un anestetico volatile. Il secondo ne mantiene lo stato di analgesia mediante la somministrazione continua di analgesici intravenosi. Nella tesi inoltre si propone un nuovo modello per descrivere le interazioni tra farmaci anestetici.

Nel capitolo introduttivo si esaminano i potenziali benefici dei controlli automatici nella pratica clinica dell’anestesia. Come esempi si considerano i casi particolari di un controllore della pressione arteriosa media (PAM) e dell’indice bispettrale (BIS) con l’ipnotico isoflurano. Si discutono inoltre sia l’architettura software che tutti gli schemi di sicurezza introdotti nella piattaforma di controllo che consentono l’applicazione di algoritmi automatici in sala operatoria.

Nel capitolo 2 si descrive il controllore ad anello chiuso che regola la componente ipnotica dello stato di anestesia del paziente. Si tratta del primo controllore basato su modelli dinamici per la regolazione dell’ipnosi con anestetici volatili che sia mai stato utilizzato su esseri umani. Il crescente uso dei monitor per il BIS nelle sale operatorie è stato lo stimolo principale per lo sviluppo del sistema di regolazione. I monitor per il BIS sono stati i primi ad aver ricevuto l’approvazione della ‘Food and Drug Administration (FDA)’ come monitor di ipnosi durante l’anestesia generale e compensano una mancanza esistente sin dalla prima anestesia generale avvenuta nel 1846.

Si riportano e si discutono infine i risultati dell’applicazione del sistema di controllo in sala operatoria. Lo schema per la regolazione del BIS è in attesa
di brevetto presso la comunità europea e negli Stati Uniti.

Nel capitolo 3 si illustra il sistema di controllo ad anello chiuso per la somministrazione continua di analgesici durante anestesia generale. Si tratta del primo controllore basato su modelli dinamici per la regolazione dello stato di analgesia del paziente che sia stato utilizzato su esseri umani. Non esiste il sensore ideale di questo sistema di controllo, poiché è improprio parlare di percezione di dolore durante anestesia totale. Il dolore è difatti per definizione una sensazione esperibile solamente da un soggetto cosciente. Con queste premesse si discute nel capitolo un sistema di controllo che mira a sopprimere gli effetti della stimolazione chirurgica sulla PAM, un possibile indicatore di una insufficiente analgesia. Lo scopo non prioritario del controllore è anche quello di regolare le concentrazioni di analgesico nel plasma predette da un modello dinamico. In questo modo si consente all’anestesista sia di dosare la somministrazione di analgesici in base ai segni clinici di una insufficiente analgesia sia di minimizzare il consumo di droga.

Nel capitolo 4 si propone un nuovo modello per quantificare le interazioni fra farmaci anestetici. Diversi modelli di interazione sono stati già proposti in diversi ambiti della biomedicina, ma non si possono estrapolare al dominio dei farmaci anestetici. Difatti l’ipotesi principale secondo la quale ogni farmaco, se somministrato singolarmente, ha un effetto sulla variabile clinica di interesse, non è soddisfatta in generale dai farmaci anestetici.

Nel capitolo 5 si riassumono i principali contributi della tesi. In particolare si evidenziano le problematiche che la ricerca futura dovrà affrontare affinché schemi di controllo automatico possano essere ordinariamente applicati in sala operatoria.
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Chapter 1

Automatic Control in Anesthesia
Foreword

The Automatic Control Laboratory at the Swiss Federal Institute of Technology (ETH) is developing a multi-task autonomous anesthesia system in collaboration with the University Hospital in Bern.

This project was supported by the strenuous commitment of excellent members of both the medical and engineering community. Heidegger believed that poetry and philosophy reside on tall, separated mountains, yet belonging to the same geographical chain. The same holds for apparently separated disciplines like medicine and engineering, which despite the different scientific methods have the common interest to improve the quality of life. Regardless of the causes of an apparent, yet perceivable incompatibility, the mutual research effort which supported this thesis contributed to bridge the gap.

The forefront control engineering concepts combined with the ultimate technology available nowadays for the anesthesiologists in the operating room made it possible for our group to achieve results which were barely conceivable just a decade ago.

But more concretely, where does the opportunity lie for disciplines like automatic control and computer science to develop new concepts and products for the clinical practice of anesthesia? Three innovating factors motivate automatic control in the clinical practice of anesthesia: new sensors for the patient monitoring, new actuators for the drug administration and new short-acting drugs. Automatic control is the scientific framework coordinating the three above cited elements.

During the initial phase of the project, several closed-loop controllers which
regulate inspired and expired anesthetic gas, $O_2$ and $CO_2$ concentrations have been used in clinical studies on humans. In this chapter two more complex controllers are discussed and compared: control of Mean Arterial Pressure (MAP) and control of hypnosis through Bispectral Index (BIS). The first controller was conceived and implemented by two former members of the institute, Marco Derighetti and Christian Frei towards completion of their Ph.D. programs. The second controller is one of the main contribution of the author of the present thesis. Both controllers use isoflurane as input, a hypnotic drug inducing hypotension. MAP was considered as the main indicator for depth of anesthesia before alternative monitoring techniques were introduced such as BIS. One of the goals of this chapter is to demonstrate how the introduction of a new sensor may go as far as to trigger radical changes in the paradigms for drug administration. BIS monitors did already open new possibilities for clinical research. It is a strong belief of the author that the benefits which we demonstrated in this chapter must also be demonstrated in the clinical practice.

Provided that hypnosis can be assessed with BIS monitors, MAP reactions to surgical stimulation may be alternatively considered as an indicator of insufficient analgesia. It was therefore natural to try and regulate MAP with intravenous opiates. The steps towards achieving this latter goal are described in chapter 3.

The following chapter also gives a qualitative overview of the supervisory functions which are necessary for the application of automatic controllers in the operating room. This topic has been the main contribution of Christian Frei's Ph.D. thesis. In particular, artifact tolerant control schemes are presented. The experimental setup and the results of the application of automatic control during clinical studies are also discussed.

This chapter appeared with minor modifications as a publication in the scientific literature as:

1.1 Introduction

1.1.1 Problem formulation

Adequate anesthesia can be defined as a reversible pharmacological state where the patient’s muscle relaxation, analgesia and hypnosis are guaranteed. Anesthesiologists administer drugs and adjust several medical devices to achieve such goals and to compensate for the effect of surgical manipulation while maintaining the vital functions of the patient. Figure 1.1 depicts the Input/Output (I/O) representation of the anesthesia problem. The components of an adequate anesthesia are labeled ‘unmeasurable’ because they must be assessed by correlating them to available physiological measurements, as depicted in Fig. 1.1.

Muscle relaxation is induced to facilitate the access to internal organs and to depress movement responses to surgical stimulations. The degree of relaxation can be estimated by measuring the force of thumb adduction induced by stimulation of the ulnar nerve or by Single Twitch Force Depression (STFD) (Viby-Mogensen et al., 2000).

Analgesia is pain relief and at present there are no specific measures to quantify it intraoperatively. A reason for this may be that it is even debatable to speak about pain perception when the subject is unconscious.
1.1 Introduction

(Prys-Roberts, 1987). Another source of complexity results from the fact that clinical signs such as tearing, pupil reactivity, eye movement and grimacing (Cullen et al., 1972) are partially suppressed by muscle relaxants, vasodilators and vasopressors.

Hypnosis is a general term indicating unconsciousness and absence of post operative recall of events occurred during surgery (Goldmann, 1988). Some authors believe there is a sharp distinction between conscious and unconscious states (Prys-Roberts, 1987). In this respect it would be improper to speak about depth of anesthesia. However, the patterns of the electroencephalogram (EEG) - which is the only non invasive measure of central nervous system activity while the patient is unconscious - show gradual modifications as the drug concentrations increase in the body. Nowadays the EEG is considered as the major source of information to assess the level of hypnosis.

Better accepted measure exist for the vital functions. Heart Rate (HR) and Mean Arterial Pressure (MAP) are considered the principal indicators for hemodynamic stability, while $O_2$ tissue saturation or endtidal $CO_2$ concentrations provide useful feedback to anesthesiologists about the adequacy of the artificial ventilation.

To achieve adequate anesthesia anesthesiologists regularly adjust the settings of several drug infusion devices as well as the parameters of the breathing system to modify the manipulated variables listed in Fig. 1.1. This is done based on some patient specific target values and the monitor readings. Thus anesthesiologists adopt the role of a feedback controller and it is natural to ask whether automatic controllers are capable of taking over and/or improving parts of such a complex decision process.

1.1.2 The benefits of feedback controllers in anesthesia

Several authors have recognized the advantages associated with the use of automatic controllers in anesthesia (Schwilden and Stoeckel, 1995; Chilcoat, 1980; O’Hara et al., 1992; Derighetti, 1999). First, if the routine tasks are taken over by automatic controllers, anesthesiologists are able to concentrate on critical issues which may threaten the patient’s safety.
Second, by exploiting both accurate infusion devices and newly developed monitoring techniques, automatic controllers would be able to provide drug administration profiles which, among other advantages, would avoid overdosing. Moreover, they may take advantage of the drug synergies, for which now a proper modeling framework was developed (Minto et al., 2000). The ultimate advantage would be a reduction in costs due to the reduced drug consumption and the shorter time spent by the patient in the Post Anesthesia Care Unit (PACU).

Further, if tuned properly, automatic controllers should be able to compensate for the interindividual variability and to tailor the drug administration profile to the particular stimulation intensity of each surgical procedure (Linkens and Hacisalihzade, 1990). Ultimately, automatic controllers can be used for research as a ‘reference’ anesthesiologist in clinical studies.

1.1.3 The challenges of the operating room

Several complexities were faced when designing the real-time platform to test closed-loop controllers in the operating room. The issues and the solutions adopted are summarized below.

- **Sensors and actuators:** To provide an adequate monitoring of the patient’s vital functions and an easy access to the drug infusion devices several sensors and actuators had to be assembled in the mobile real-time platform depicted in Fig. 1.2.

- **Safety critical system:** All the implemented closed-loop controllers use physiological signals which are potentially corrupted by artifacts. They may result either from routine manipulation or calibration of the measuring devices and may cause, if not considered in the control schemes, considerable damage to the patient (Frei, 2000). A supervisory system and fault tolerant controllers were embedded in the real-time platform to detect sensor failures and/or other abnormal operations. A more detailed description of these safety features of the platform will be given in a later section.

- **Model uncertainty:** A major source of difficulty results from the high uncertainty associated with the published models for the drug
distribution and effect. Nevertheless, anesthesiologists are able to compensate for interindividual variability by tailoring the drug administration to the single subject’s needs, therefore guaranteeing an adequate performance across the population. In order to reproduce this, feedback controllers must be designed with robust and/or adaptive techniques. Robust techniques tend to lead to controllers for the ‘worst case’ situation, which tends to make them sluggish. Adaptive schemes rely on the excitability of the input signal, which is often limited by ethical constraints. Our approach was to use both data collected from ordinary patients during anesthesia and data acquired from young healthy volunteers for the design and the validation of the proposed control strategies.

- **Clinical validation:** The improvements for the clinical practice and the patient’s care which are envisioned from the use of automatic controllers in anesthesia cannot be quantified unless extensive clinical validation is performed. Therefore the ETH project has been put on solid foundations by establishing a close cooperation between a
Automatic Control in Anesthesia clinic (University Hospital of Bern) and an anesthesia workplace manufacturer (Dräger Medizintechnik, Lübeck, Germany). Among other advantages, the partnership with the hospital enabled us to acquire data directly from young healthy volunteers for model identification. The support from the industrial partners provided us with the latest available technology on the market.

Up to now, six different control strategies have been tested by the ETH-University Hospital team on more than 150 patients during general anesthesia. These controllers regulate $O_2$, $CO_2$, inspired and expired anesthetic gas concentrations in the breathing system as well as MAP and depth of hypnosis derived from the EEG (Derighetti et al., 1996; Frei, Derighetti, Morari, Glattfelder and Zbinden, 2000; Sieber et al., 2000; Gentilini et al., In press, 2001.; Derighetti, 1999; Frei, 2000).

1.1.4 Closed-loop control of anesthetic effect

Among the several controllers presented in the last section, two Single Input Single Output systems (SISO) extracted from the Multiple Input Multiple Output (MIMO) control problem depicted in Fig. 1.1 will be described extensively here: Mean Arterial Pressure (MAP) and Bispectral Index (BIS) control. Both feedback systems use the volatile anesthetic isoflurane as input and aim at controlling the anesthetic effect.

Several reasons motivate MAP control during surgery (Frei, 2000; Derighetti, 1999). MAP decreases with increasing isoflurane concentrations in the internal organs. As such, MAP can be considered to be a direct measure of the anesthetic effect. Beyond that, hypotension is also induced to minimize blood losses and increase surgical visibility (Furutani et al., 1995). Moreover, maintaining MAP within an acceptable physiological range guarantees adequate perfusion to internal organs. Finally, suppressing MAP reactions to surgical stimuli enhances the patient’s safety. MAP is measured invasively by a catheter placed in the radial artery. The signal is transferred to the monitors by a transducer and sampled at a frequency of 128 Hz. Every repositioning of the patient, as well as calibration of the transducer and flushing of the catheter to prevent blood clots leads to an artifact in the measured signal. Artifacts are suppressed with a scheme discussed later.
Hypnosis can be assessed with the Bispectral Index (BIS Index, Aspect Medical System, Newton, Massachusetts). The BIS index is derived from the EEG by combining the higher order spectra of the signal with other univariate indicators such as Spectral Edge Frequency (SEF) and Median Frequency (MF) (Schwilden et al., 1987; Schwilden et al., 1989; Shüttler and Schwilden, 1995). This combination of indicators is necessary since, for instance, SEF and MF can provide an estimate of the hypnotic state at deep levels but are likely to fail in the region of light sedation (Ghouri et al., 1993; Kochs et al., 1994). BIS can reveal, unlike simple Fourier analysis, the synchrony of cortical brain signals which characterizes unconsciousness (Rampil, 1998). BIS values lie in the range 0-100, where 100 is associated with the EEG of an awake subject and 0 denotes an isoelectric EEG signal. BIS predicts accurately return of consciousness (Doi et al., 1997; Glass et al., 1997; Kearse et al., 1994; Sebel et al., 1995) and is the first clinical monitor for hypnosis which to date has received FDA clearance. BIS has been developed and validated based on EEG recordings of 5000 subjects. More than 600 peer-reviewed articles and abstracts provide a clinical evaluation of BIS.

The modeling issues and the control design will be outlined for both controllers. The additional safety issues required for the application in the operating room will also be described. Clinical results will be discussed for both controllers.

1.2 Modeling

The model required for control has to account for two qualitatively different systems: the medical devices (actuators and sensors) and the physiology involving drug distribution, metabolism and the effect in the human body.

1.2.1 The respiratory system

A schematic drawing of the respiratory system depicted at the bottom of Fig. 1.2 is given in Fig. 1.3. A pump forces the air into the patients’ lungs while unidirectional valves impose a fixed orientation for the circulation of
Figure 1.3: Schematic representation of the closed-circuit breathing system. Typical ranges for the parameters of the respiratory system (see Eq. (1.1) for a detailed description) are: \( Q_0 = 1-10 \text{ l/min} \), \( f_R = 4-25 \text{ l/min} \), \( V_T = 0.3-1.2 \text{ l} \), \( V = 4-6 \text{ l} \), \( \Delta Q = 0.1-0.5 \text{ l/min} \), \( C_0 = 0-5 \% \), expressed as isoflurane volume percent in the breathing mixture.

The fresh gas stream enters on one branch and excessive air leaves on the other. This gas flow through the system leads to a constant flush. If a high fresh gas flow is used (\( Q_0 > 4 \text{ l/min} \)), the dynamics introduced by the respiratory system may be neglected since a change in the fresh gas composition is effective for the patient almost immediately. During minimal flow anesthesia (\( Q_0 < 1 \text{ l/min} \)) the fresh gas flow only compensates for gas taken up by the patient and the eliminated \( CO_2 \) through the absorber. At such low flows the system is economically more efficient and safer for the patient. In fact, due to recirculation, the patient breathes a gas mixture at almost constant humidity and temperature. The expired gases are now recirculated, which introduces considerable dynamics. A first principles model of the minimal flow breathing system was derived to capture the behaviours of the system in detail (Derighetti, 1999). A simplified description giving the same prediction accuracy can be obtained by considering the respiratory system as a well stirred tank (Frei, 2000). Inspired concentrations depend on the vaporizer fresh anesthetic gas concentrations \( C_0 \) and the subject’s
breathing parameters through the following equation:

$$V \frac{dC_{\text{insp}}}{dt} = Q_0 C_0 - (Q_0 - \Delta Q) C_{\text{insp}} - f_R (V_T - \Delta) (C_{\text{insp}} - C_1) \quad (1.1)$$

where $V$ [l] is the volume of the respiratory system. $C_1$ [%] is the alveolar concentration or endtidal concentration, measured as volume percent of the breathing mixture. $f_R$ [1/min] is the respiratory frequency, $V_T$ [l] is the tidal volume, $\Delta$ [l] is the physiological dead space. $\Delta Q$ [l/min] represents the losses of the breathing circuit through the pressure relief valves. $Q_0$ and $C_0$ [%] are the fresh gas flow and its anesthetic concentration entering the respiratory circuit, respectively. $C_d$ is the manipulated variable in our control system. We will refer to $C_0$ as the “vaporizer setting” in the following sections.

### 1.2.2 Modeling the effect of anesthetic drugs

The physiological mechanisms regulating drug distribution and drug effects are only partially known. Therefore first principles modeling is almost impossible. Thus one has to select from approximate first principles physiological models (Bischoff, 1975), black-box identification schemes (Jacobs, 1988), and knowledge based modeling. All approaches exhibit certain drawbacks. In physiological models parameters are highly uncertain and collected from different sources where experiments may have been performed under very different conditions. Black-box models and knowledge based models suffer from poor extrapolation properties.

For the design of both BIS and MAP controllers, we used physiology based models. They consist of a pharmacokinetic (PK) part describing the drug distribution into the internal organs and a pharmacodynamic (PD) part describing the drug effect on the physiological variables of interest. The structure of the PK part is common to both controllers, since both use isoflurane as input. The PD part differs in the two models and will be discussed in the next two sections.

Any PK model consists of differential equations resulting from mass balances for the drug around different compartments (Jacquez, 1985). For the generic
i^{th} compartment we may write (Zwart et al., 1972):

\[ V_i \frac{dC_i}{dt} = Q_i(C_a - C_{i,o}) - k_i(C)C_i \]  

(1.2)

\[ C_{i,o} = C_i/R_i \]  

(1.3)

where \( Q_i \) is the blood flow bathing the organ, \( V_i \) is the distribution volume of the drug, \( k_i \) is the elimination rate, \( R_i \) is the apparent partition coefficient which macroscopically describes drug absorption and metabolism as a ratio between internal \( (C_i) \) and outflow \( (C_{i,o}) \) concentration (Bischoff, 1975). \( C \) is the vector of drug concentrations in the different compartments and \( C_a \) is the drug concentration in the arterial pool. Since the pharmacological properties of isoflurane were extensively documented (Eger II, 1984; Warren and Stoelting, 1986; Yasuda, Lockhart, Eger, Weiskopf, Johnson, Freire and Faussolaki, 1991; Yasuda, Lockhart, Eger II, Weiskopf, Liu, Laster, Taheri and Peterson, 1991), some of the parameters in Eqs (1.2,1.3) were derived from the literature. The others were estimated from the data collected during general anesthesia with isoflurane. For further details on the identification procedure the reader is referred to the published literature (Derighetti, 1999; Frei, 2000).

Inspired and endtidal concentrations are measured on-line and provide a reliable indication of the patient’s drug uptake. This represents a clear advantage over intravenous drugs, for which no measure of drug concentration in the central compartment is available. This advantage was exploited in both control schemes by imposing constraints on endtidal concentrations to prevent overdosing.

In our models ventilation and blood flow are described as nonpulsatile phenomena. Since the equilibration time of the drug is greater than the respiratory cycle and the period of HR, this assumption does not affect performance of the controllers.

### 1.2.3 Modeling for control of MAP

To model the PD effect of isoflurane on MAP, we assumed that the reaction of the hemodynamic system to the drug does not change during prolonged administration (Derighetti, 1999; Frei, 2000; Warren and Stoelting, 1986).
In other words no time varying phenomena due to sensitation or tolerance to isoflurane were considered. Even though HR is known to be strongly coupled with MAP, it was not taken directly into account into our model. Several tachycardic episodes have been reported during isoflurane anesthesia and may suggest the need to model those effects (Shimosato et al., 1982). However, it is not clear whether those episodes depend on beta sympathetic activation of baroreflex activity. In fact, at moderate to deep levels of isoflurane anesthesia, two clinical investigations have reported contradictory results concerning the activity of the baroreflex, leaving the issue unresolved (Seagard et al., 1983; Kotrly et al., 1984).

The modeling structure describing the hemodynamic effects of halothane (Zwart et al., 1972) was adapted to the characteristics of isoflurane. While halothane decreases Cardiac Output (CO), reducing the perfusion to internal organs (Gelman et al., 1984; Smith and Schwede, 1972), isoflurane decreases mainly systemic resistance through dilatation of the blood vessels (Eger II, 1984). We assumed that MAP and CO can be described through the following PD relationship:

\[ MAP = \frac{Q_a(C)}{\sum_{i=1}^{N} g_i(C)} \quad (1.4) \]

where \( g_i \) represents the conductivity of the \( i^{th} \) organ, increased by the presence of isoflurane and \( Q_a = \sum_{i=1}^{N} Q_i \) represents CO (Derighetti, 1999; Frei, 2000). Conductivities \( g_i \)s are assumed to depend exclusively on the anesthetic concentration in the same compartment whereas \( Q_a \) is assumed to depend on the arterial (A), gray matter (G) and myocardial (M) concentrations through the affine relationships:

\[ Q_a = Q_{a,0} (1 + a_A C_A + a_G C_G + a_M C_M) \quad (1.5) \]
\[ g_i = g_{i,0}(1 + b_i C_i). \quad (1.6) \]

\( Q_{a,0} \) and \( g_{i,0} \) are the baseline CO and conductivity in the \( i^{th} \) organ, respectively. According to the previous discussion, the effects of isoflurane concentrations are more pronounced in Eq. (1.6) than in Eq. (1.5) (Frei, 2000).

MAP must be kept within physiological limits during anesthesia despite surgical stimulations. Therefore, a physiological model describing the effects of skin incision, skin closure and intubation on the systemic circulation was derived (Derighetti, 1999; Frei, 2000). Surgical stimulations activate the
sympathetic part of the autonomous nervous system, as other situations like stress, infection and hemorrhages do. The sympathetic system triggers a neural and a humoral reaction. The first causes the release of norepinephrine in the synaptic cleft, whereas the second is associated to the discharge of norepinephrine and epinephrine from the adrenal medulla into the blood stream. The two reactions show significantly different time constants, one in the order of few seconds and the other in the order of a minute, which is the characteristic time constant of blood circulation. It is expected that the MAP reactions show the same distinct time constants. These effects have been experimentally observed during our clinical studies. A typical example where both effects are clearly visible after a tetanus stimulation is shown in Fig. 1.4. MAP measurements expressed as deviations from the value before stimulation are plotted versus time immediately after the stimulus for one patient. The solid line represents the prediction of the model (1.5,1.6). This model was validated during clinical studies and the possibility of suppressing the effects of surgical stimulation by a feedforward compensation with isoflurane were investigated (Frei, Derighetti, Morari, Glattfelder and Zbinden, 2000).

Even though the model for MAP was extensively validated, it still contains a great amount of uncertainties. These may result from the different types and sites of surgical stimulation and the different subjects' sensitivities to pain (Petersen-Felix et al., 1998).

1.2.4 Modeling for control of BIS

To model the PD effects of isoflurane on BIS, we enrolled 20 consenting volunteers and have put them under general anesthesia with isoflurane. At the time there were no published PD models describing the effect of isoflurane on BIS. For a more detailed description of the study design, the reader is referred to chapter 2 of the present thesis.

We assumed that the overall dynamic model from isoflurane inspired concentrations to BIS is limited by the drug distribution to the organs. Once the drug faces the receptors or effect site, we can assume that the binding occurs instantaneously. Then, at the effect site, the relation between BIS and local anesthetic concentrations is represented by a static nonlinearity. None of the compartments of the PK model could be considered the ef-
Figure 1.4: MAP deviations (○) from values before stimulation are plotted versus time after a tetanus stimulus for one subject at 0.5 % endtidal concentration of isoflurane. The neuronal (first peak) and humoral (second peak) components of the MAP reaction are distinguishable from the plot. Adapted from the literature (Frei, 2000).

... effect compartment in light of the arguments above. Therefore an artificial effect compartment was added to the model to compensate for this hidden dynamics. The effect compartment can be regarded as an additional compartment with negligible volume attached to the central compartment. This assumption ensures that its presence does not perturb the mass balance equations of the PK model. Effect site concentrations are related to endtidal concentrations by a first-order delay:

\[
\frac{dC_e}{dt} = k_{eo}(C_1 - C_e).
\]  

(1.7)

The parameter \(k_{eo}\) is referred to as the equilibration constant for the effect
site. As PD relationship we adopted the classical $E_{\text{max}}$ model:

$$\Delta BIS = \Delta BIS_{\text{MAX}} \frac{C^2}{C^2_0 + EC_{50}^\gamma}$$  \hspace{1cm} (1.8)

where

$$\Delta BIS = BIS - BIS_0$$ \hspace{1cm} (1.9)
$$\Delta BIS_{\text{MAX}} = BIS_{\text{MAX}} - BIS_0.$$ \hspace{1cm} (1.10)

$BIS_0$ is the baseline or awake state value, $BIS_{\text{MAX}}$ represents the minimum achievable $BIS$. $EC_{50}$ represents the concentration at the effect site for which the effect is half of the maximum achievable. $\gamma$ represents the subject’s sensitivity to small concentration changes at the effect site. It can be regarded as an index of the model nonlinearity. We assumed $BIS_0 = 100$ and $BIS_{\text{MAX}} = 0$ since high concentrations of isoflurane lead to an isoelectric EEG. In such cases $BIS = 0$.

The modeling assumptions together with the available identification procedure for the effect site compartment are discussed with more details in the literature (Yasuda, Lockhart, Eger II, Weiskopf, Liu, Laster, Taheri and Peterson, 1991; Schnider et al., 1994). It is worth mentioning that the variability of the estimated PD parameters in our study is one order of magnitude greater than for the PK parameters (Gentilini et al., In press, 2001). This fact is also confirmed by off-line analysis of the data collected during the clinical evaluation of the BIS controller. Figure 1.5 displays the effect of isoflurane concentrations at the effect compartment on BIS for two different patients during clinical studies. Together with the single individual’s PD relationships, the PD function identified from the population of volunteers is shown. In the left figure a patient who behaves very similarly to the population of volunteers is recognizable, whereas in the right plot a great difference is observed. In particular, it seems to be extremely difficult to achieve BIS values under 40 for the patient in the right plot, unless a large amount of isoflurane is used. On-line estimation of a single individual’s PD characteristics and, in particular, deviations from the behaviour of the average subject of the population would improve the controller performance. Adaptive schemes which would use this information are currently studied in our research project.
In this section the control design to regulate MAP and BIS is discussed.

1.3.1 MAP Control

Control of MAP is performed by means of three Observer Based State Feedback (OBSF) controllers whose interconnection is illustrated in Fig. 1.6, where $y_1$ and $y_2$ represent MAP and endtidal isoflurane concentrations, re-
respectively. The underlying idea of the control structure is that the main

\[ V_1,\text{ref}, \quad V_2,\text{ref} \]

controller \( C_1 \) regulating MAP is active under normal conditions. However, constraints have to be imposed on \( y_2 \). An upper bound \( y_{2,\text{ref}}^* \) is needed because high isoflurane concentrations may lead to hypotonic crisis, cardiac arrhythmias, or even cardiac arrest. To comply with the upper limit the override controller \( C_2^{**} \), which is in itself a complete OBSF controller, was introduced. The minimum selector applied to the control signals of \( C_1 \) and \( C_2^{**} \) ensures that the upper limit \( y_{2,\text{ref}}^* \) is complied with.

A minimum endtidal concentration \( y_{2,\text{ref}}^* \) must also be guaranteed to prevent light anesthesia and awareness. Therefore we also introduced an override controller \( C_2^* \) to ensure a minimum endtidal concentration. The stability analysis of the override structure was done according to the published literature (Glattfelder et al., 1983; Glattfelder and Schaufelberger, 1988).

Figure 1.6: Block diagram of the override structure to control MAP. \( y_1 \) and \( y_2 \) denote MAP and endtidal concentration measurements, respectively. \( C_1 \) regulates MAP under normal conditions whereas \( C_2^{**} \) and \( C_2^* \) enforce the upper and lower limit for endtidal concentrations. \( u \) represents the vaporizer setting. Adapted from the literature (Frei, 2000).
The classical state feedback controller with observer (Kwakernaak and Sivan, 1972) was modified with the additional blocks represented in Fig. 1.16 (Derighetti, 1999). A feedforward compensation term for MAP as well as integral action were added for better setpoint tracking and to compensate for the effect of surgical stimulations and modeling errors, respectively. The input saturation shown in Figs 1.6 and 1.16 limits the fresh gas concentrations between 0% and 5%, expressed as isoflurane volume fraction in the fresh gas flow. Therefore, an anti-windup compensation was added to cope with the input constraints, which was not depicted in Fig. 1.16 for the sake of simplicity. The parameters of the controller were obtained as the solution of a linear quadratic regulator (LQR) problem (Bryson and Ho, 1975). The controllers were parametrized with the fresh gas flow $Q_0$, the patient’s weight and the respiratory frequency $f_R$ such that it is possible to compute the controller parameters on-line without going through the whole LQR design process.

### 1.3.2 BIS Control

To control BIS we adopted the cascaded Internal Model Control (IMC) depicted in Fig. 1.7, where the master controller regulates BIS and the slave controller regulates endtidal concentrations. The model of the patient

![Figure 1.7: Block diagram of the cascaded Internal Model Control (IMC) structure to control BIS. $y_1$ and $y_2$ denote BIS and endtidal concentration measurements, respectively. The master controller $Q_1$ provides endtidal concentration references $y_2, r_{ref}$ to the slave controller $Q_2$. The saturation block after $Q_1$ was introduced to enforce upper and lower limits for $y_2$.](image)
is split in two parts. The PK model $\hat{P}_2$ relating inputs at the vaporizer $u$ to endtidal concentrations $y_2$ and the effect compartment model $P_1$ relating $y_2$ to $y_1$ or BIS. The overall model is nonlinear, where the nonlinearity is represented by the PD relationship relating effect site concentrations to BIS (Gentilini et al., In press, 2001.). According to Fig. 1.7, the master controller $Q_1$ provides endtidal concentration reference values $y_{2,\text{ref}}$ to the slave controller. This control loop forces $y_2$ to reach the reference value $y_{2,\text{ref}}$ specified by the master loop.

The theoretical background and the tuning guidelines for IMC control systems are reported in the literature (Morari and Zafiriou, 1989). Input saturation was also added to the parallel model $\hat{P}_2$ as an anti-windup prevention. The saturation block after $Q_1$ limits endtidal concentration references between 0.4% and 2.5%. Constraints on $y_{2,\text{ref}}$ ensure that the limits for $y_2$ are not violated, but also represent a clear limitation on the controller's bandwidth. To compensate for this, anesthesiologists are able to enlarge or narrow the range of the constraints at their convenience during anesthesia.

The parallel model in the master loop is a linearization of the nonlinear PD model around a reference concentration. This configuration proved to be more robust with respect to PD parametric uncertainties than the full nonlinear model. The offset concentrations in the block diagram were omitted for the sake of simplicity. The transfer functions of the parallel models $\hat{P}_2$ and $P_1$ were obtained by using the average parameters identified from the population of volunteers. The transfer functions of the IMC blocks $Q_2$ and $Q_1$ were chosen as the filtered inverses of the nominal models $\hat{P}_2$ and $P_1$ (Morari and Zafiriou, 1989).

The choice of a cascaded arrangement with IMC controllers contributed significantly to the acceptance of the controllers in the operating room. In fact, the cascade arrangement mimics the procedure adopted by anesthesiologists if they were asked to control BIS manually. Namely, due to lack of clinical experience in controlling the hypnosis through BIS values, an anesthesiologist would first target a specific value for endtidal concentrations. Then she/he would adjust the endtidal concentration references on the basis of the BIS values. In the developed control scheme both tasks are achieved at the same time. Also, the design is accomplished by tuning just two parameters, which have a direct, clear interpretation. These parameters affect the approximate closed-loop time constant of the slave and
master controller, respectively. Further, in the ideal case when there is no plant-model mismatch, the closed-loop trajectory tracks reference changes with no overshoot, therefore preventing overdosing. The time constants of the IMC filters were set to achieve nominal settling times for such controllers (defined as 90% of the steady-state value) equal to $t_s = 2$ min for the endtidal controller and $t_s = 4$ min for the overall BIS controller.

Another advantage of the IMC strategy is that the control transfer functions can be adjusted on-line when the operating conditions of the closed-circuit breathing system are changed. This is not unusual during surgery since $f_R, V_T, Q_0$ are often modified for several reasons. For instance, short periods at high flows ($Q_0 \geq 5 \text{ l/min}$) are normally used when a quick wash-out of the drug is needed towards the end of the operation. Further, increasing alveolar ventilation $f_R(V_T - \Delta)$ is a standard procedure to reduce high levels of endtidal CO$_2$ which result from an increased metabolism (Chapman et al., 1985). If respiratory parameters are changed by the anesthesiologist at any time during automatic mode, the supervisory system will update the model $P_2$ and the $Q_2$ block.

1.4 Clinical validation of the controllers

1.4.1 MAP control

For the evaluation of the MAP controller forty ASA-class I to III patients aged 20 to 65 scheduled for elective abdominal, orthopedic, thoracic or neuro-surgery are enrolled in the study. The goal is to compare MAP control performed by anesthesiologists with automatic MAP control. The study is about to be completed. In all clinical validations of MAP control which we will discuss, the lower $y_{2,\text{ref}}^{\text{low}}$ limit for endtidal concentrations was set to 0.4%. The upper limit $y_{2,\text{ref}}^{\text{up}}$ may vary from 1% to 1.5% depending on the surgical procedure. MAP values around the MAP measured at the arrival of the patient in the operating room were used as targets. For half the patients chosen at random, closed-loop administration of isoflurane is switched off roughly in the middle of the surgery period. From there on, isoflurane is manually administered by the anesthesiologist. For the second half of the patients, the opposite is done.
Figure 1.8: Automatic MAP regulation during liver surgery. The first plot from above depicts MAP and MAP references, respectively. The second plot represents endtidal concentration measurements $y_2$ together with the upper and lower limits $y_{2,ref}^+$ and $y_{2,ref}^-$. The third plot represents the vaporizer settings during the study. In the fourth plot the active controller is depicted, where -1 denotes $C_2^*$ is active, +1 denotes $C_3^{**}$ is active and 0 denotes $C_1$ is active. Note that the upper override controller becomes active when heavy surgical stimulation starts at $t = 50$ min. Adapted from the literature (Frei, 2000).

The clinical performance is evaluated based on several criteria such as the duration of periods with MAP within ± 10% of the target value, number and type of critical incidents in both groups. These are periods with MAP $< 65$ mmHg, systolic blood pressure BP $> 160$ mmHg or HR $> 110$ bpm.

Figures 1.8, 1.9 and 1.10 show a clinical evaluation of the MAP controller. In all figures the upper plot represents the MAP profile during the study. The second plot represents the endtidal concentrations $y_2$ together with the
upper $y^{**}_{2,\text{ref}}$ and lower $y^{**}_{2,\text{ref}}$ limits. The third and fourth plots represent
the vaporizer settings and the active controller, respectively. According to
notation in Fig. 1.6, -1 denotes that $C_2$ is active, +1 denotes that $C^{**}_2$ is
active and 0 denotes that $C_1$ is active.

In Fig. 1.8 the MAP profile under automatic control during a liver surgery
is represented. The controller is able to achieve good performance during
the periods of light surgical stimulations occurring at $t = 38$ min and $t =
89$ min. Note that during the period of light stimulation ($t = 20-35$ min)
the override selector often switches between the MAP controller $C_1$ and
the lower endtidal $C^*_2$ even though endtidal concentrations lie within the
acceptable range. Presumably, this is a result of the particular sensitivity of
the patient’s MAP to isoflurane during the unstimulated period. In this case
the controller $C_1$ would tend to reduce isoflurane settings and consequently
endtidal concentrations below the accepted limit. At roughly $t = 50$ min,
a heavy surgical stimulation occurs. To compensate for this, an endtidal
concentration larger than $y^{**}_{2,\text{ref}}$ would be required. This activates the upper
override controller $C^{**}_2$, as depicted in the fourth plot of Fig. 1.8.

Figure 1.9 shows a comparison between manual and automatic control. Up
to $t = 192$ min anesthesia was conducted manually. According to the anes-
thesiologist, during this phase just minor adjustments of the vaporizer set-
ing were needed. At $t = 210$ min automatic control starts. This phase is
dominated by a heavy disturbance starting at approximately $t = 220$ min
and a period of good regulation from $t = 250$ min on. Note from the second
plot in Fig. 1.9 that the controller tends to make more use of the bandwidth
of allowed endtidal concentrations than the anesthesiologist, also as a re-
result of the heavier surgical stimulations in the second part of the operation.
Figure 1.10 shows a clinical evaluation where the controller was able to sup-
press the effect of surgical stimulations occurring at $t = 82$ min and $t = 115$
min, respectively. The period between $t = 50$ min and $t = 80$ min was not
characterized by any significant stimulations. During this phase the lower
endtidal controller was active to deliver a minimum amount of isoflurane.

The following conclusions can be drawn from the above discussion. The
controller is successfully able to compensate for light disturbances as shown
in Fig. 1.8. The limited control action and the fast disturbance dynam-
ics seriously limit the ability to compensate for heavy disturbances. These
limitations also apply for manual control. Therefore we expect that the dif-
Figure 1.9: Comparison of manual and automatic regulation of MAP. Automatic control starts at minute $t = 210$ min. For a detailed description of the variables in each plot, see the caption of Fig. 1.8. Note in the second plot that automatic control makes use of a wider bandwidth of endtidal concentrations than the anesthesiologist. This presumably results from the heavier surgical stimulations in the second part of the operation. Adapted from the literature (Frei, 2000).

The difference between manual and automatic control will not be substantial. An intuitive way for improving blood pressure regulation is to provide the controller with information about major future disturbances like skin incision (Frei, Derighetti, Morari, Glattfelder and Zbinden, 2000). This approach is now being tested in first pilot studies.

1.4.2 BIS control

Forty ASA-class I to III patients aged 20 to 65 scheduled for elective abdominal, orthopedic, thoracic or neuro-surgery are enrolled in the clinical
evaluation of the BIS controller. The goal of the study is to determine whether closed-loop titration of isoflurane to target specific values of BIS improves the quality of anesthesia. Time to eyes opening after interruption of drug administration, average time spent by the patient in the PACU will be recorded together with episodes where BIS was outside the range 30-70. These periods indicate excessive and insufficient level of hypnosis, respectively. The study is in progress. Figure 1.11 shows the performance of the controller during a discus hernia removal. To the best of the authors’ knowledge, this is the first model-based closed-loop controller for hypnosis assessed with BIS using volatile anesthetics which has been tested on humans. The controller was able to keep BIS in the range 40-50 and to
follow changes in the reference signal appropriately. The performance of the slave controller is better than the master, as apparent when comparing the first and second plot in Fig. 1.11. This is expected, since the model uncertainty is lower for the PK model than for the PD model. Further, endtidal measurements are less noisy than the BIS.

Figure 1.12 shows another clinical validation of the controller. The automatic controller was started at $t = 70$ min. At $t = 80$ min the fresh flow rate was decreased from $Q_0 = 3$ l/min to $Q_0 = 1$ l/min to minimize anesthetic consumption. The supervisor recognizes the changes in the breathing system and updates the model in the controller. As a result, the vaporizer setting increased immediately to a higher level, which compensates for the slower dynamics at low flow conditions. Note also that the input at the
1.4 Clinical validation of the controllers

Figure 1.12: The plots illustrate the clinical study as described in the caption of Fig. 1.11. Automatic control was started at \( t = 70 \) min and the fresh gas flow rate was reduced from \( Q_0 = 3 \) l/min to \( Q_0 = 1 \) l/min at \( t = 80 \) min. The supervisor implements instantaneously a higher vaporizer input to compensate for the slower dynamics of the actuator at low flows.

vaporizer does not change across the switch from manual to automatic control at \( t = 70 \) min. A bumpless transfer procedure was designed to provide a smooth transition between manual and automatic anesthetic administration. The mathematical details of the procedure are reported in chapter 2.

Interesting conclusions can be drawn when comparing the performance of the MAP and the BIS controller. Namely, surgical stimulations are not affecting BIS - and therefore the hypnotic state - as much as they do affect MAP. This is expected, since consciousness is depressed with lower anesthetic concentrations than the stress response and particularly hemodynamic reactions. The question is then whether isoflurane should be used...
to regulate BIS or MAP. Isoflurane being a hypnotic, it would seem more natural to use it to regulate BIS. However, this also depends on the anesthesiologists' confidence in the BIS values. A meaningful control objective would be to administer isoflurane to regulate BIS while maintaining MAP within specified limits.

### 1.5 Supervisory functions

The supervisory functionality may be regarded as the superposition of all the necessary functions that have to be wrapped around the basic feedback control algorithms to make them routinely applicable in the operating room.

Even though the need for supervisory functionality for automatic control application in anesthesia has clearly been recognized by a number of researchers, not all of them implemented them in real practice (Furutani et al., 1995; Kwok et al., 1997). Often just a brief outline of the necessary supervisory functions is presented (Fukui and Masuzawa, 1989; Martin, 1994; Martin et al., 1992; O'Hara et al., 1992; Isaka and Sebald, 1993; Woodruff, 1995). A supervisory system was implemented in our real-time platform according to the scheme represented in Fig. 1.13. Four main layers can be identified.

**D Input and output conditioning:** The measurements pass an input conditioning stage as they enter the anesthesia system. This includes preprocessing of the signals, selection of the most trusted one out of a set of multiple measurements and rejection of measurement artifacts. Similarly, the control signals pass through a comparable output conditioning stage. Typical tasks of this part are the shaping of test inputs for Fault Detection and Isolation (FDI), the min-max selection of an override controller or the switch from manual to automatic control.

**C Process information:** At this stage all the data available about the state of the process are stored, including controller states. Typically, this information is stored in data banks. From there the data are accessed for storage or for display.
Figure 1.13: The different layers of supervisory functions. At the lower level physiological measurements and output for the actuators pass through a signal preprocessing stage. For instance artifacts in the measurements are rejected during this phase. At the top level, the Man Machine Interface is represented. Adapted from the literature (Frei, 2000).

B Algorithmic layer: This incorporates feedback controllers, Supervisor Logic Control (SLC), Fault Detection and Isolation (FDI) algorithms, as well as decision support functions. The separation into layers B1 and B2 separates dynamic from logic control. At this stage, for instance, transition conditions are checked to allow the anesthesiologist to switch to automatic control. FDI functions are responsible for detecting faults in the system. This may include equipment faults like disconnected sensors or leaks as well as the detection of critical physiological patient states like excessive blood losses. Decision Support (DS) makes suggestions to the anesthesiologist on how to optimize the anesthetic procedure. It provides information that can not be directly read off from monitors. Typical examples are the display of the esti-
mated time required for the patient to wake up after termination of drug application or the estimated concentration of anesthetics in the different compartments.

A Man Machine Interface (MMI): This is the most user oriented layer and it is therefore drawn as the top layer of the supervisory structure. Every information from the system to the anesthesiologist and vice versa has to pass through the MMI. The MMI is typically implemented by a graphical user interface (GUI) but any acoustic alarm is also part of the MMI. As an example the control panel adopted during BIS control is depicted in Fig. 1.14.

![Operating panel for closed-loop regulation of hypnosis](image)

Figure 1.14: Operating panel for closed-loop regulation of hypnosis. (a) Central panel which displays parameters of the breathing system, BIS and the actual control action; (b) buttons for the switch between passive, manual and automatic control; (c) buttons to inform the controller about significant events such as skin incision, skin closure and intubation; (d) BIS controller panel, where the reference BIS is selected together with tolerable limits for the endtidal anesthetic concentration; (e) information about active controller and reliability of both BIS and endtidal concentration measurements.
The detailed discussion of all the supervisory functions is beyond the scope of the present chapter but can be found in the literature (Frei, 2000). Instead we will focus on a particular aspect of the supervisory system which is the treatment of measurement artifacts.

### 1.5.1 Artifact tolerant controllers

![Diagram](image)

Figure 1.15: Example of an untreated artifact occurring during automatic control of endtidal anesthetic concentrations. In the upper plot, endtidal isoflurane concentration references (— —) and measurements (— —) are plotted. In the lower plot, vaporizer settings are represented. Note that the short disconnection of the sampling line is interpreted by the controller as an absence of anesthetic in the breathing system. It therefore reacts by injecting instantaneously a large amount of anesthetic which delays the settling time of the step response. Adapted from the literature (Frei, 2000).

Several authors listed the undesirable implications of non proper artifacts
handling during closed-loop control in anesthesia for the patient (Ruiz et al., 1993; Reid and Kenny, 1987; Fukui and Masuzawa, 1989). A minor consequence is illustrated in Fig. 1.15. Here a model-based endtidal controller is supposed to lower endtidal isoflurane concentrations from 1.3% to 0.7% as indicated by the dashed line. During this maneuver an automatic calibration of the monitor occurs during which a zero value is provided for the concentration measurement. This sudden change in the controlled output causes the controller to fully open the vaporizer. Although the artifact terminates after 20 s, enough isoflurane has been supplied to the system to considerably overshoot and prolong the maneuver. Fortunately, this situation only deteriorates the controller performance but there are no critical consequences for the patient here. On the other hand artifacts in the blood pressure signal might lead to sharp decreases of blood pressure during MAP control. An example of such critical transients is documented by Fukui and Masuzawa (Fukui and Masuzawa, 1989). Luckily, we have not encountered such a situation.

Figure 1.16: Artifact tolerant control schemes for Observer Based State Feedback (OBSF) controllers. The nonlinear functions ψ and ψ₁ exclude the residuals which are corrupted by artifacts and which may lead to serious degradation of the controller’s performance. Adapted from the literature (Frei, 2000).

Before presenting our solution to the artifact problem we investigate how artifacts deteriorate controller performance. Figure 1.16 represents a classi-
1.5 Supervisory functions

In developing the strategy we will work with a linear time invariant approximation of the system represented by the state space matrices $A, B, C, D$. In Fig. 1.16 $v(t)$ and $w(t)$ represent process and measurement noise, respectively. $\delta(t)$ represents the artifacts. The observer serves to estimate the states $\hat{x}$ of the system. The matrix $L$ for update of the observer states can be computed considering process and measurement noise characteristics, e.g. with a Kalman filter design.

The artifacts $\delta(t)$, unlike white measurement or process noise, affect the controller in two ways. First, through the output injection matrix $L$ artifacts lead to a mismatch between observer states and system states. Second, they lead to an offset of the integral part of the controller. This mismatch between controller states and reality can be viewed as a controller wind-up (Kothare et al., 1994). A natural remedy to prevent artifacts from degrading the controller performance is to make sure that the artifacts $\delta(t)$ do not enter the observer equations.

In a stochastic framework the error signal $e_y(t) = y(t) - \hat{y}(t)$ represents a vector valued zero mean and white stochastic process (Bar-Shalom and Fortmann, 1988). If $v(t)$ and $w(t)$ are zero mean white noise processes and an artifact occurs, $e_y(t)$ is not zero mean but has a mean of $\delta(t)$. Thus the detection of an artifact based on the innovations signal $e_y(t)$ is equivalent to detecting a sudden shift in the mean of $e_y(t)$. The test for the zero mean hypothesis may be formulated as a statistical decision based on the actual value of $e_y(t)$.

In case of an artifact the corresponding output injection vector is set to $L_i = 0$ which prevents the artifact from entering the observer equations. The statistical decision may be represented by a diagonal nonlinear block $f(e_y(t))$ multiplying the innovations $e_y(t)$. That is:

$$f_i(e_{y_i}(t)) \cdot e_{y_i}(t) = \begin{cases} e_{y_i}(t), & e_{y_i}(t) \leq T_i \\ 0, & e_{y_i}(t) > T_i \end{cases}$$

(1.11)

where $T_i$ is a specific threshold value. With a more general nonlinearity

$$\psi(e_y(t)) = \text{diag}(\psi_1(e_{y_1}(t)), \cdots, \psi_p(e_{y_p}(t)))$$

(1.12)
the observer dynamics become:
\[ \dot{x}(t) = Ax(t) + Bu(t) + L\psi(e_y(t))e_y(t). \quad (1.13) \]

Typically \( \psi_i(e_y(t)) \) is such that \( \psi_i(0) = 1 \) and \( \psi_i(-\infty) = \psi_i(\infty) = 0 \). An analogous approach may be taken to exclude artifacts from the integrator equation.

With the nonlinear modification introduced in Eq. (1.13) the stability of the feedback system must be checked anew. To do this, the system can be transformed into the following form:
\[ e_y = G(s)e + z_1 \quad (1.14) \]
\[ \dot{e} = \Delta(e_y) + z_2 \quad (1.15) \]

where \( G(s) \) incorporates the linear time invariant parts of the closed-loop system and \( \Delta \) contains the nonlinear weighting functions. Using Integral Quadratic Constraints (IQC) one can check the stability of Eqs (1.14,1.15) even when time varying or uncertain systems are included in the \( \Delta \)-block.

The nonlinear modifications \( \psi_i(e_y) \) of the output injection have to be chosen such that the performance of the observer does not suffer in the artifact free case. More precisely they must be chosen such that the normal noise on the signal \( e_y \) does not lead to an inactivation of the observer corrections.

The artifact suppression scheme was extensively tested during the clinical validation of the model-based endtidal controller as well as for MAP and BIS control. In this latter case the concepts were adapted to the particular structure of the cascaded IMC controller. Figure 1.17 shows typical cases where artifacts were properly detected without performance deterioration. In particular, the lower plot in Fig. 1.17 shows the correct behaviour for an artifact lasting for approximately 5 min.

### 1.6 Experimental setup

When it comes to the routine application of automatic controllers on patients, considerable attention must be paid to a proper Hardware/Software (HW/SW) platform. In the early phase of the project the controllers were
Figure 1.17: In both plots measured inspired (——) and endtidal concentrations (— —) as well as endtidal concentrations predicted by the observer (— • —) are represented. The plots demonstrate the successful suppression of artifacts during sensor calibration and disconnection, where no endtidal measurements are available. Adapted from the literature (Frei, 2000).

implemented under Modula II on an MS DOS supported industrial PC with the necessary A/D and D/A conversion boards (Derighetti, 1999). This platform suffered from a number of shortcomings, such as poor support of real-time and multi tasking features, lack of software components to design adequate user interfaces and compiler limitations.

Currently a target (VME PowerPC) - host (PC) computer system provides the hardware basis for the experimental platform (Frei, 2000). The operating system X Oberon from the Robotics Institute of ETH provides the required real-time and multi task features (Wirth and G utknecht, 1993). The applications are implemented using the object oriented programming language Oberon, a member of the Pascal-Modula family (Kottmann et al.,
Making use of the object oriented technology a framework has been developed which efficiently allows to write new control applications.

The platform is depicted in Fig. 1.2. The compact integration of the computer system equipped with a touch-screen on a standard CiceroEM anesthesia workstation from Dräger Germany contributes significantly to the general acceptance of this prototype system in the operating room. Also, the platform is endowed with an emergency shut-down button which cuts any active controller off and transfers the regulation of the breathing system to the anesthesiologist through manual dosing. Recently an i.v. pump has been integrated for the continuous infusion of analgesics.

The design of the MMI aimed at reproducing closely the standard monitoring systems for anesthesia. This way anesthesiologists are able to run closed-loop controllers without any engineering support. An example of an operating panel was already presented in Fig. 1.14.
Chapter 2

Feedback Control of Hypnosis
Foreword

In this chapter the model-based closed-loop control system which regulates hypnosis with the volatile anesthetic isoflurane is discussed in detail. Hypnosis is assessed by means of the Bispectral Index (BIS), a processed parameter derived from the electroencephalogram (EEG). Isoflurane is administered through a closed-circuit respiratory system. The model for control was identified on a population of 20 healthy volunteers. It consists of three parts: a model for the respiratory system, a pharmacokinetic (PK) and a pharmacodynamic (PD) model to predict BIS at the effect compartment. A cascaded Internal Model Controller (IMC) is employed. The master controller compares the actual BIS and the reference value set by the anesthesiologist and provides expired isoflurane concentration references to the slave controller. The slave controller maneuvers the fresh gas anesthetic concentration entering the respiratory system.

Several advantages of the model-based approach which revealed to be a key factor for the success of this controller are worth to be mentioned:

- the controller is designed to adapt to different respiratory conditions
- anti-windup measures protect against performance degradation in the event of saturation of the input signal
- fault detection schemes in the controller cope with BIS and expired concentration measurement artifacts.

The results of 4 clinical studies performed in the operating room on humans are presented in the thesis. Two of them were already discussed in chapter
1. In the following chapter two other clinical validations are presented. The control structure is under patent pending in both the European Community and the United States of America.

This chapter can be found with minor modifications as a publication in the scientific literature as:

2.1 Introduction

2.1.1 Assessment of anesthesia

We already discussed the definition of anesthesia as an adequate combination of hypnosis, analgesia and muscle relaxation in the introductory section of chapter 1. We briefly outlined how to measure muscle relaxation and we pointed out the difficulties in assessing analgesia intraoperatively. This latter aspect will be discussed in more details in chapter 3. This chapter will be devoted to the methods to measure and control the patient’s hypnosis intraoperatively.

Hypnosis is associated with unconsciousness and absence of post operative recall of intraoperative events (Goldmann, 1988). With the electroencephalogram (EEG) the brain activity can be measured non-invasively. Anesthetics change the pattern of EEG. These changes can be quantified and correlate with the drug concentration. The EEG has been used as a measure of depth of hypnosis. However, several difficulties are associated with the use of EEG as a measure of the degree of unconsciousness (McEwen et al., 1975). Unlike the electrocardiogram (ECG), the EEG has no cyclic patterns and statistical techniques must be used to extract useful information. Moreover, while most anesthetics affect the EEG, they do so in different ways (Stanski, 1990): for instance, high doses of opiates produce a slow paced, high voltage EEG whereas hypnotic agents induce ‘burst suppression’, short periods of time where the EEG is isoelectric (Muthuswamy et al., 1999).

2.1.2 Closed-loop drug administration and BIS

Several feedback controllers for anesthesia have been proposed in the literature. The effectiveness of such controllers strongly depends on the reliability of the physiological signal to be controlled, as in the case of muscle relaxation (Mahfouf and Linkens, 1997; Mahfouf and Linkens, 1998; Ross et al., 1997; Ritchie et al., 1985). Concerning analgesia, where no reliable measure exists, it was noted that the patient’s autonomic responses to painful stimulations are present both in the awake state and with hypnotic
2.1 Introduction

and analgesic agents (Pinsker, 1986). A pragmatic task would be to deliver a sufficient amount of drugs to obtund them. Hemodynamic variables such as Mean Arterial Pressure (MAP), Cardiac Output (CO) and Heart Rate (HR) have been considered in this respect (Isaka and Sebald, 1993). MAP control is also crucial during surgery to improve surgical visibility and to guarantee adequate perfusion to internal organs (Furutani et al., 1995). Since most volatile hypnotics also depress MAP (Warren and Stoelting, 1986), yet by different mechanisms of action (Murray et al., 1992; Monk, 1988), they were used as input variables in several feedback schemes (Prys-Roberts and Millard, 1990; Millard et al., 1988; Frei, Gentilini, Derighetti, Glattfelder, Morari, Schnider and Zbinden, 1999).

Concerning hypnosis, several univariate parameters like Spectral Edge Frequency (SEF) and Median Frequency (MF) can be extracted from the spectral characteristics of the EEG and have been used as controlled outputs in a closed-loop system (Shüttler and Schwilden, 1995; Schwilden et al., 1987; Schwilden et al., 1989). All the mentioned quantities can provide an estimate of the hypnotic state at deep levels. However, they are likely to fail in the region of light sedation (Ghouri et al., 1993; Kochs et al., 1994). Bispectral analysis computes higher order spectra of EEG which can reveal phase couplings of single waveforms. Together with multivariable statistical analysis this feature is the main foundation for the Bispectral Index (BIS, Aspect Medical Systems Inc. Newton, Massachusetts). Thus BIS is an EEG derived parameter which provides a continuous reliable estimate of hypnotic state (Rampil, 1998). BIS predicts accurately return of consciousness (Doi et al., 1997; Glass et al., 1997; Kearse et al., 1994; Sebel et al., 1995) and it has been developed and verified based on the EEG recordings of 5000 subjects. To date, more than 600 peer-reviewed articles and abstracts describe a clinical evaluation of BIS. More than 2,500,000 patients have been monitored with BIS across the globe. BIS has been successfully used as a controlled variable in a closed-loop application with the intravenous agent propofol (Mortier et al., 1998).

2.1.3 Goal of this study

The goal of our research is to design a closed-loop system to control the BIS with isoﬂurane. The problem is fundamentally different from that when
intravenous agents are used for control. On the one hand, the use of volatile anesthetics introduces the complexity of the respiratory system. On the other hand expired concentrations provide a useful indication of the drug concentrations in the body.

To the authors’ best knowledge this work describes the first closed-loop system to control BIS with volatile anesthetics. The controller based on a model identified from experiments on humans.

In this chapter we first describe the volunteer study which provided the data necessary to identify a dynamic model to predict BIS. It is followed by an analysis of the data and a description of the model structure. Subsequently, the control design is outlined. Notwithstanding its increasing popularity, BIS is still under development and evaluation. Therefore we must guarantee the patient’s safety in those situations where BIS is corrupted by artifacts and therefore not unreliable as a feedback signal. To achieve this, a cascade arrangement was used which maintains expired anesthetic concentrations between acceptable limits. When switching from manually administered anesthetic to closed-loop control the continuity of the control action is guaranteed providing a smooth transition. Moreover, we discuss the procedures which guarantee safe performance of the controller in the presence of artifacts in both BIS and expired concentration measurements.

Finally, the results obtained from two particular tests of the controller on patients are presented and discussed.

### 2.2 Volunteer study

The experiments were designed to explore the effects of the hypnotic isoflu-rane and the analgesic alfentanil on several clinical end-points such as BIS, raw EEG and hemodynamic variables. Another goal of the study was to determine the reactions of such end-points to experimental painful stimuli, which may be used to define depth of anesthesia (Petersen-Felix et al., 1996).
2.2 Volunteer study

2.2.1 Demographic data

Twenty consenting volunteers of physical status ASA I were enrolled for the study. The age group considered was 25 ± 3 years, weight was 68 ± 13 kg. The subjects were randomly assigned to two groups. In the first group alfentanil targeted concentrations were varied whereas endtidal concentrations of isoflurane were kept constant. In the second group isoflurane was varied and alfentanil was kept constant.

2.2.2 Experimental setup

Zipprep® electrodes were secured on the subjects in frontal position, as recommended by the manufacturer of the BIS monitor. Raw EEG and BIS were monitored with Aspect A-1000 monitor (Aspect Medical Systems Inc. Newton, Massachusetts). The electrodes’ impedance was kept under 3 kΩ. The sampling frequency of the raw EEG signal was 128 Hz. The sampling frequency of BIS was 5 s. Arterial pressure was measured invasively with a catheter cannula inserted into the radial artery. Electrocardiogram (ECG), O₂ saturation in the tissues, gas concentrations in the breathing system were recorded at 100 Hz with a Compact AS/3 monitor (Datex-Ohmeda Division. Helsinki. Finland). Inspired and endtidal O₂, CO₂, sevoflurane and isoflurane concentrations were also calculated during every breathing cycle and stored as volume percentages by Compact AS/3 monitor. Muscle relaxation was monitored continuously with the Train Of Four (TOF) procedure. A high frequency (128 Hz) event marker was used to track significant events during the study such as the begin and end of each painful stimulation, occurrence of movement responses and blood sampling. Hemodynamic data, as well as raw EEG and BIS were acquired with Labview 5.0 under Windows NT for off-line analysis.

2.2.3 Study design

Before induction, baseline values were recorded for approximately 10 min while the subjects were breathing pure O₂ with a face mask. General anesthesia was induced by the single breath technique with a mixture of 7 %
sevofurane in 60% N₂O. Bolus doses (0.15 mg/kg body weight) of mivacurium were administered after loss of eyelid reflexes to facilitate intubation. Respiratory parameters during assisted ventilation were adjusted to maintain endtidal CO₂ partial pressures between 35 and 40 mmHg. Fresh gas flow was set to 6 l/min. Body temperature was kept in the range 36.5-37°C.

Hypnosis was maintained by continuous administration of isoflurane with the autonomous closed-circuit respiratory circuit Cicero (Dräger Medizintechnik GmbH, Lübeck, Germany). Alfentanil was delivered through the infusion pump Harvard Apparatus 22. Targeting infusion policies algorithms maintained a constant level of predicted drug concentration in the plasma. The infusion policies were computed with the software STANPUMP under DOS 1.

Each volunteer was kept at 7 different steady-state combinations of hypnotic and analgesic, with each phase lasting for approximately 20 min. Each combination is defined by a constant level of predicted plasma concentration of alfentanil and a constant level of endtidal concentration of isoflurane. When the physiological variables reached the steady-state values, different experimental stimuli were applied in a randomized sequence. Arterial samples of isoflurane and alfentanil were collected. The sampling occurred during both the transient phases when the target concentrations of both the analgesic and the hypnotic were modified and during steady-state.

At the end of the study, alfentanil infusion was stopped and the fresh gas concentration of isoflurane was set to zero at the same time. The subjects were extubated as soon as they opened their eyes after their names were called.

2.3 Modeling

The model developed for control consists of three interacting parts: a description of the respiratory system, a model for the uptake and distribution of isoflurane and an effect compartment model to describe the time course of the BIS. The model for the respiratory system was already presented in chapter 1. The dynamics of the closed-circuit respiratory system are

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1STANPUMP is freely available from the author, Steven L Shafer, M.D., Anesthesiology Service (112A), PAVAMC, 3801 Miranda Ave, Palo Alto, CA. 94304.
2.3 Modeling

<table>
<thead>
<tr>
<th>Parameter</th>
<th>mean±SD [min⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{12}$</td>
<td>1.26 ± 0.204</td>
</tr>
<tr>
<td>$k_{13}$</td>
<td>0.402 ± 0.055</td>
</tr>
<tr>
<td>$k_{14}$</td>
<td>0.243 ± 0.072</td>
</tr>
<tr>
<td>$k_{15}$</td>
<td>0.0646 ± 0.0414</td>
</tr>
<tr>
<td>$k_{20}$</td>
<td>0.0093 ± 0.0137</td>
</tr>
<tr>
<td>$k_{21}$</td>
<td>0.210 ± 0.082</td>
</tr>
<tr>
<td>$k_{31}$</td>
<td>0.0230 ± 0.0156</td>
</tr>
<tr>
<td>$k_{41}$</td>
<td>0.00304 ± 0.00169</td>
</tr>
<tr>
<td>$k_{51}$</td>
<td>0.000500 ± 0.000119</td>
</tr>
</tbody>
</table>

Table 2.1: Mammillary rate constants of the PK model published by Yasuda and colleagues.

described by Eq. (1.1).

2.3.1 Distribution model

Isoflurane is carried to the internal organs by the systemic circulation and most volatile anesthetics depress cardiovascular activity. As a result, the uptake and distribution at high concentrations of isoflurane might be slower than at low concentrations. Several publications report the pharmacologic properties of isoflurane (Eger II, 1981; Eger II, 1984). Isoflurane decreases arterial pressure to the same extent as halothane and Enflurane do (Warren and Stoelting, 1986; Murray et al., 1992). However, with isoflurane the decrease is the result of a reduction in systemic resistance (Graves et al., 1974) whereas for halothane it is mainly a result of a lowered Cardiac Output (CO) (Prys-Roberts et al., 1974; Lynch, 1986). In fact, at 2.6% endtidal concentrations of isoflurane, the CO is reduced by only 10% relative to the baseline value (Collins, 1996). Therefore we assume that the distribution characteristics of isoflurane are not affected by hypotension.

Yasuda and colleagues have identified a mammillary compartmental model for the distribution of isoflurane (Yasuda, Lockhart, Eger II, Weiskopf, Liu, Laster, Taheri and Peterson, 1991). The compartments are depicted in Fig. 2.1. The mammillary rate constants are reported in Tab. 2.1.
Figure 2.1: The mammillary compartment model published by Yasuda and colleagues (Yasuda, Lockhart, Eger II, Weiskopf, Liu, Laster, Taheri and Peterson, 1991). The concentrations in the central compartment (1) represent endtidal concentrations, i.e. the concentrations at the end of the expiration cycle or equivalently alveolar concentrations.

In their experimental setup young healthy volunteers received a mixture composed by 1% sevoflurane, 0.6% isoflurane, 34.4% $O_2$ and 64% $N_2O$ for 30 min. Synergies between volatile anesthetics at the distribution level can be neglected (Vuyk, 1997). Endtidal samples were collected during the administration, in the following 23 hours and every morning for the next 6-7 days. The number of compartments was established by statistical testing on the model residuals to avoid overparametrization. A posteriori, the compartments were associated with groups of internal organs on the basis of their time constants. Compartments 2 and 3 have fast dynamics and are associated with the Vessel Rich Group and the Muscles, respectively. Compartments 3 and 4 are notably slower and are associated with fat compartments. By using the published partition coefficients of isoflurane (Yasuda et al., 1989), it is possible to estimate the volumes $V_j$ and the perfusing
2.3 Modeling

Table 2.2: Volumes of the mammillary compartments as published by Yasuda and colleagues.

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Volumes [L] (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.3±0.71</td>
</tr>
<tr>
<td>2</td>
<td>7.1±2.5</td>
</tr>
<tr>
<td>3</td>
<td>11.3±5.6</td>
</tr>
<tr>
<td>4</td>
<td>3.0±0.7</td>
</tr>
<tr>
<td>5</td>
<td>5.1±4.1</td>
</tr>
</tbody>
</table>

The volumes of the compartments are reported in Tab. 2.2. Based on visual inspection of the data we assumed that alfentanil does not modify the distribution characteristics of isoflurane. Therefore we adopted the distribution model described by Yasuda and colleagues as a PK model. With Eq. (2.1) the mass balance for isoflurane in the central compartment is:

\[
\frac{dC_1}{dt} = \sum_{j=2}^{5} \left( k_{1j} C_j \frac{V_j}{V_1} - k_{1j} C_1 \right) + \frac{f_R (V_T - \Delta)}{V_1} (C_{insp} - C_1). \tag{2.3}
\]

For the general \( j^{th} \) compartment \((j \neq 2)\) we obtain:

\[
\frac{dC_j}{dt} = k_{1j} C_1 \frac{V_1}{V_j} - k_{1j} C_j \tag{2.4}
\]

whereas for \( j = 2 \)

\[
\frac{dC_2}{dt} = k_{12} C_1 \frac{V_1}{V_2} - k_{21} C_2 - k_{20} C_2. \tag{2.5}
\]

An open-loop validation of the model with the data collected in our volunteer study is represented in Fig. 2.2. Inspired concentrations during the study were used as input to the PK model to predict endtidal concentrations. The comparison with measured endtidal concentrations is reported.
Figure 2.2: Open-loop validation of the Yasuda PK model for the distribution of isoflurane. The administration profile for subject 6 is depicted. The upper (---) and lower (—) point series represent measured inspired and endtidal concentrations, respectively. The thick solid line (—) represents the model prediction for endtidal concentrations.

in Fig. 2.2, showing excellent agreement between measurements and model predictions. The model is able to predict endtidal concentrations with sufficient accuracy also during closed-loop experiments, as we will discuss in the last section of the chapter.

2.3.2 Effect compartment modeling

The adopted PK model is not able to describe the time course of BIS with isoflurane. As an example, let us consider the administration profile of isoflurane for volunteer 11 and the BIS time course, as depicted in Fig. 2.3. Blank data windows in Fig. 2.3 correspond to periods where the subject
Figure 2.3: In the upper plot, the BIS profile for subject 11 during the study is plotted. In the lower plot, the corresponding PK profile of isoflurane is depicted. The upper (- - -) and lower (-----) point series represent measured inspired and endtidal concentrations, respectively.

received experimental painful stimuli. Those periods were excluded from this analysis since they belong to the disturbance response of the subject.

In Fig. 2.4 BIS is plotted versus measured endtidal and second compartment predicted concentrations. If time is considered in the plot of the endtidal concentrations, the data describe a clockwise hysteresis. In the second plot, they describe a counterclockwise hysteresis. This demonstrates that the dynamics of BIS must lie between the time course of the concentrations in these two compartments. This also means that, when endtidal concentrations are at steady-state, the concentrations at the effect compartment are not at steady-state yet. These delays can be attributed to transportation at the site of effect as well as diffusion resistances.
To compensate for this unmodeled dynamics, an effect compartment (Schnider et al., 1994) was linked to the central compartment, as shown in Fig. 2.1. The effect compartment does not represent any physiological organ or group of organs in the human body. Rather it models the drug transportation delays from the lungs to the site of effect. By assumption, the volume of the effect compartment is negligible. As a consequence, its introduction in the model does not affect the mass balances in Eqs. (2.3,2.5). Effect compartment concentrations are related to concentrations in the central compartment by the following first order model:

$$\frac{dC_e}{dt} = k_{e0}(C_1 - C_e).$$  \hspace{1cm} (2.6)
At the effect compartment an $E_{\text{max}}$ model is assumed as the PD model:

$$\Delta BIS = \Delta BIS_{\text{MAX}} \frac{C_s^\gamma}{C_s + EC_{50}^\gamma}, \quad (2.7)$$

where

$$\Delta BIS = BIS - BIS_0, \quad (2.8)$$

$$\Delta BIS_{\text{MAX}} = BIS_{\text{MAX}} - BIS_0. \quad (2.9)$$

$BIS_0$ is the baseline or awake state value, $BIS_{\text{MAX}}$ represents the $BIS$ theoretically achievable with infinite isoflurane concentrations at the effect compartment. $EC_{50}$ and $\gamma$ are the two parameters of the PD model that have to be identified. $EC_{50}$ represents the subject’s sensitivity for the drug whereas $\gamma$ is a measure of the degree of nonlinearity in Eq. (2.7). We assumed $BIS_0 = 100$ and $BIS_{\text{MAX}} = 0$.

The equilibration constant of the effect compartment $k_{e0}$ as well as the PD constants $EC_{50}$ and $\gamma$ can be estimated by collapsing the hysteresis loop in the plane of $BIS$ versus effect site concentrations. Loop collapsing was transformed into two nested nonlinear regression problems. First a tentative value for $k_{e0}$ is assumed. Then the optimal $EC_{50}$ and $\gamma$ were estimated as:

$$\{EC_{50, \text{opt}}, \gamma_{\text{opt}}\} = \arg \min_{(EC_{50}, \gamma)} \sigma^2 \quad (2.10)$$

where

$$\sigma^2 = \frac{1}{N-1} \sum_{i=1}^{N} \left[ BIS_i - \hat{BIS}_i \right]^2. \quad (2.11)$$

In the previous equation $BIS_i$ denotes the $i^{\text{th}}$ measurement and $BIS_i$ denotes the corresponding model prediction. $N$ is the number of BIS measurements collected for that particular volunteer. If we denote the minimum of $\sigma^2$ as $\sigma_{\text{opt}}^2$, we can iterate on $k_{e0}$ such that:

$$k_{e0, \text{opt}} = \arg \min_{k_{e0}} \{\sigma_{\text{opt}}^2\}.$$  

Estimates of the measured endtidal concentrations at a given BIS measurement were obtained by linear interpolation, which introduces negligible error. The results of the identification scheme are reported in Tab. 2.3.
Table 2.3: Estimated $k_{e0}$, $EC_{50}$ and $\gamma$ for each volunteer. The last row reports the estimates obtained from the pooled analysis.

<table>
<thead>
<tr>
<th>Volunteer</th>
<th>$k_{e0}$ [min$^{-1}$]</th>
<th>$EC_{50}$ [vol %]</th>
<th>$\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tr>
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<td>1.453</td>
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<td>0.7032</td>
<td>1.677</td>
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<td>9</td>
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<td>0.7494</td>
<td>1.000</td>
</tr>
<tr>
<td>10</td>
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<td>0.4950</td>
<td>1.369</td>
</tr>
<tr>
<td>11</td>
<td>0.3684</td>
<td>0.9220</td>
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<tr>
<td>12</td>
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<td>1.590</td>
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<tr>
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<td>0.5976</td>
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<tr>
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<td>1.000</td>
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<td>0.6130</td>
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</tr>
<tr>
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</tr>
<tr>
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<td>0.7699</td>
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<td>20</td>
<td>5.000</td>
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<td>1.402</td>
</tr>
<tr>
<td>pooled</td>
<td>0.3853</td>
<td>0.7478</td>
<td>1.534</td>
</tr>
</tbody>
</table>
for each volunteer of the study. The improvement in the fit introduced by the effect compartment is depicted in the left plot of Fig. 2.5 for subject 11. At the effect compartment the hysteresis observed in the left plot of Fig. 2.4 has almost completely disappeared. For the optimization we used $0 < k_{e0} \leq 5 \, \text{[min}^{-1}]$ and $0 < \gamma \leq 5$ as constraints.

The upper constraints were active at the end of the optimization for subjects 10, 19 and 20. Subjects 10 and 19 received anesthesia at constant isoflurane input during the whole study. This did not produce significant BIS changes. Subject 20 received high doses of isoflurane and BIS remained constantly low. Those subjects are excluded from further discussion.

The average $k_{e0}$ in the population was $0.9480\pm1.0831 \, \text{[min}^{-1}]$ ($\mu \pm \sigma$), an estimate biased towards high values, as a result of the $k_{e0}$ values identified for subjects 4, 5, 7. Table 2.3 also reports the optimal parameters for the pooled analysis, where the data from all subjects of the study were analyzed. The $k_{e0}$ value obtained from the pooled analysis is $0.3853 \, \text{[min}^{-1}]$, indicating a more robust estimate with respect to outlying subjects. It is worth noticing that the coefficient of variation for $k_{e0}$ ($\sigma/\mu = 1.1426$) is one order of magnitude higher than any of the coefficients of variation for the PK parameters reported in Tab. 2.1. Therefore special care must be used to tune the controllers to be robust to uncertainties in the PD parameters.

The average $EC_{50}$ in the population was $0.7495\pm0.1771 \, \text{[vol} \%]$, while the result from the pooled analysis is $0.7478$. The negligible difference between the two estimated values is a consequence of the symmetric distribution of the single individual parameters around their mean. For $EC_{50}$ the coefficient of variation was lower ($\sigma/\mu = 0.2362$) than for the $k_{e0}$ estimate. The average $\gamma$ in the population was $1.60\pm0.5437$, while the result from the pooled analysis was $1.534$. In this case the mean value is slightly influenced by the high values estimated for subjects 11, 13, 16 and 17. The data points together with the fitted PD relationship are depicted in the right plot of Fig. 2.5. In this case the beneficial effects of the effect compartment model for the fit improvement are hidden by the interindividual variability.

Under different experimental conditions which deserve attention when comparing the results, Olofsen and Dahan have identified an effect compartment model to describe the effects of isoflurane on the BIS from endtidal concentration measurements (Olofsen and Dahan, 1999). They report $k_{e0} = 0.217$...
Figure 2.5: In the left plot, BIS values versus effect site concentrations for subject 11. In the right plot, BIS values versus effect site concentrations in the pooled analysis. In both plots, the solid line (—) represents the estimated PD relationship.

A recent study has reported an average of $k_{e0}$ estimated from population data, where $EC_{50} = 0.6\%$ and $\gamma = 5.8$ as mean values identified from the population examined. The higher average $k_{e0}$ estimated with our data might be the result of several factors. First, our data set was collected from volunteers and not from patients. Second, we explored a broader range of isoflurane endtidal concentrations (0.4%-2.2% compared with 0.6%-1.6%) and we performed randomized changes between the levels to be explored. Finally, a reason may be the use of the analgesic alfentanil in our study. In particular, a comparison of the two estimated $k_{e0}$ values would suggest that alfentanil accelerates BIS equilibration. Although this hypothesis would have relevant medical implications, it was not considered relevant for the purpose of control design. In addition, in our data set alfentanil neither increased nor decreased BIS consistently. An example is depicted in Fig. 2.6. For this particular subject, none of the changes both in targeted as well as in mea-
2.4 Control design

sured alfentanil concentrations produced a noticeable BIS variation. These considerations led us to exclude alfentanil in our model for BIS control.

Figure 2.6: In the lower plot, alfentanil target (—) and measured (○) plasma concentrations for subject 4. In the upper plot, BIS is represented at the corresponding time instants. Isoflurane endtidal concentrations were kept at 1 % all throughout the study.

2.4 Control design

The overall dynamic system from vaporizer setting to concentrations at the effect compartment is a series connection of two linear time invariant systems. Both systems are Single Input Single Output (SISO). Let us denote
the system were vaporizer settings and endtidal concentrations are the input and output, respectively. From Eqs (1.1,2.3,2.5) we have:

\[
A_2 = \begin{bmatrix} -k_R & k_{1R} & 0 & 0 & 0 & 0 \\ k_{10} & -k_1 & k_{21} & 0 & 0 & 0 \\ 0 & k_{12} & -k_{20} & k_{21} & 0 & 0 \\ 0 & k_{13} & 0 & -k_{31} & 0 & 0 \\ 0 & k_{14} & 0 & 0 & -k_{41} & 0 \\ 0 & k_{15} & 0 & 0 & 0 & -k_{51} \end{bmatrix} \quad (2.14)
\]

\[
B_2^T = \begin{bmatrix} Q_0/V \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad (2.15)
\]

\[
C_2 = \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad (2.16)
\]

where

\[
k_R = (Q_0 - \Delta Q + f_R (V_T - \Delta))/V \quad (2.17)
\]

\[
k_{1R} = f_R (V_T - \Delta)/V \quad (2.18)
\]

\[
k_{10} = f_R (V_T - \Delta)/V_1 \quad (2.19)
\]

\[
k_1 = k_{10} + k_{12} + k_{13} + k_{14} + k_{15}. \quad (2.20)
\]

The above system is connected in series with the effect compartment described by Eq. (2.6), where the input is the endtidal concentration and the output \( y_1 \) is the BIS. We have:

\[
\dot{x}_1 = A_1 x_1 + B_1 y_2 \quad (2.21)
\]

\[
y_1 = f(x_1) \quad (2.22)
\]

where \( f(\cdot) \) denotes the nonlinearity in Eq. (2.7).

The control structure to regulate BIS was already discussed in chapter 1. In the following we will refer to the notation introduced in Fig. 1.7.
The transfer functions of the $P_2$ and $P_1$ blocks are:

$$P_2(s) = \frac{Q_0 k_{10} (s + k_{21} + k_{20}) \prod_{j=3}^{5} (s + k_{j1})}{V (s + k_{R}) \prod_{j=1}^{5} (s - \lambda_j) - k_{1R} k_{10} (s + k_{21} + k_{20}) \prod_{j=3}^{5} (s + k_{j1})}$$

(2.23)

$$P_1(s) = \frac{k_{c0}}{s + k_{c0}}$$

(2.24)

where $\lambda_j$ are the eigenvalues of the mammillary compartmental matrix. It can be shown that $\lambda_j < 0 \quad \forall \ j = 1, \ldots, 5$ (Jacquez and Simon, 1993). The transfer function of the parallel model $\hat{P}_2$ was obtained from Eq. (2.23) with mean parameters from Tabs 1 and 2. Similarly, $\hat{P}_1$ was obtained from Eq. (2.24) with $k_{c0}$ from the pooled analysis whose results are reported in Tab. 3. The transfer functions of the IMC blocks $Q_2$ and $Q_1$ are the filtered inverses of the nominal plants:

$$Q_2(s) = P_2(s) \hat{P}_2^{-1}(s)$$

(2.25)

$$Q_1(s) = P_1(s) \hat{P}_1^{-1}(s)$$

(2.26)

with IMC filters chosen as:

$$F_i(s) = \frac{1}{(\lambda_i s + 1)^{n_i}}.$$  

(2.27)

We set $n_2 = 3$ and $n_1 = 2$ to guarantee strict properness of the controllers. Since both $P_2$ and $P_1$ are minimum-phase, the full plant inverses were taken in Eqs (2.25,2.26). The model for the master loop is a linearized version of Eq. (2.21,2.22) around the reference concentration $C_e = EC_{50}$. The linearization constant is:

$$k_m = \left( \frac{-BIS_0 \gamma (C_e/EC_{50})^{\gamma} 1}{[1 + (C_e/EC_{50})^{\gamma}]^{2} C_e} \right)_{C_e=EC_{50}} = \frac{BIS_0 \gamma}{4 \ EC_{50}}.$$  

(2.28)

With the average values form the pooled analysis we obtain $k_m = -51.28$, where the concentrations are expressed in volume percent. The time constants of the IMC filters in Eq. (2.27) were set to $\lambda_1 = 1.0$ min and $\lambda_2 = 0.7$ min, respectively. This particular choice of the parameters guarantees nominal settling times of $t_s = 2$ min for the endtidal controller and $t_s = 4$ min for the overall BIS controller, as we already discussed in chapter 1.
2.5 Implementation

The controllers were implemented in a discrete state space form. The sampling times of the controllers were set to $\Delta T = 5$ s, corresponding to the sampling frequency of the BIS. Three additional features were implemented to improve performance and cope with the safety requirements in the operating room.

2.5.1 Smooth transfer

When the controller is switched on, a smooth transfer procedure must be guaranteed to provide an optimal administration profile for the patient. That is, the first control action of the controller must be equal to the last input action specified during manual control. This is automatically guaranteed in our real-time platform if reference endtidal concentrations are set equal to measured concentrations ($y_{2,ref} \equiv y_2$) during open-loop. Let us assume that the block diagram is open after the output of the block $Q_2$ and let us denote as $u_{con}$ and $u_{man}$ the inputs specified by the block and the anesthesiologist, respectively. We have:

$$u_{con} = Q_2 \left[ y_{2,ref} - (y_2 - \tilde{y}_2) \right] = Q_2 \tilde{P}_2 u_{man} = F_2 u_{man}. \quad (2.29)$$

Analogously, we must guarantee that the output of the $Q_1$ block converges to the measured endtidal concentration. To do so, we set $y_{1,ref} \equiv y_1$. Then:

$$y_{2,ref} = Q_1 \left[ y_{1,ref} - (y_1 - \tilde{y}_1) \right] = Q_1 \tilde{P}_1 y_2 = F_1 y_2. \quad (2.30)$$

Since for both filters $F_i(0) = 1 \ (i = 1, 2)$, $u_{con}$ will converge to $u_{man}$ and $y_{1,ref}$ to $y_2$, provided the input $u_{man}$ is asymptotically constant. The anesthesiologist is not allowed to switch from manual to closed-loop control before the input computed by the controller has reached the value she/he imposed with a tolerance of $\pm 10\%$. The controller will be ready to be started within a time equal to the settling time of the filter $F_2$. During this phase the time constants of the IMC filters are temporarily reduced to shorten the waiting time.

The presented initialization scheme was accepted by anesthesiologists at this stage of the project, because $u_{man}$ is not often changed prior to the
beginning of surgery. A more accurate bumpless transfer procedure which would allow perfect tracking of \( u_{con} \) within a negligibly small time will be published in a future work.

### 2.5.2 Respiratory parameters update

The parameters of the closed-circuit respiratory system \( f_R, V_T, Q_0 \) may be changed during surgery for several reasons.

As an example, surgical stimulations may induce arousal reactions in the patient which are not promptly captured by the BIS, since BIS values displayed on the monitor at a given time result from calculations on the previous 15-30 seconds of raw EEG data. In this case short periods at high flows \( (Q_0 \geq 5 \text{ l/min}) \) are often used to guarantee a faster equilibration of endtidal concentrations because of the higher mass flow rate of fresh anesthetic. In this manner the arousal reaction is compensated.

In another scenario it may be necessary to reduce high levels of \( CO_2 \) in the blood pool by increasing alveolar ventilation \( f_R(V_T - \Delta) \) (Chapman et al., 1985).

For these reasons we allow the respiratory parameters to be changed by the anesthesiologist at any time during automatic mode. To enhance the controller performance, we automatically update the model \( P_2 \) and the \( Q_2 \) block in Eqs (2.23) and (2.25), respectively. The effects of a fresh flow change and the consequent model update were already presented and discussed in Fig. 1.12.

### 2.5.3 Artifact tolerant controllers

Occasionally, the measured signals used for feedback control (endtidal isoflurane concentrations and BIS values) are corrupted by artifacts. Such artifacts may be introduced in the concentration measurements by device calibration and/or disconnection of the sampling line. BIS artifacts might come from the high impedance of the electrodes, corruption of the EEG with the electromyography signal (EMG) and accidental disconnection of the elec-
Several authors (Reid and Kenny, 1987; Ruiz et al., 1993; Frei, 2000) have recognized that such artifacts must be handled appropriately not to seriously degrade the controller’s performance or threaten the life of the patient. An elegant framework to design artifact-tolerant controllers for the observer-based feedback controllers was proposed (Frei, Bullinger, Gentilini, Glattfelder, Sieber and Zbinden, 2000; Frei, 2000). The error residuals between measurements and the observed predictions serve as a basis for the artifact detection and prediction problem. The same approach for artifact handling cannot be applied in this case. In fact, even though parallel models are used in the block diagram depicted in Fig. 1.7, they are not observers.

However, the error residuals may still be useful in the artifact detection problem for endtidal concentration measurements. In fact, in this particular case artifacts result from the calibration of the measurement device and temporary disconnection of the sampling line and/or the Y piece. The first situation is automatically triggered by the measuring device, whereas the others may occur during repositioning of the patient. In all cases $y_2 \to 0$ and consequently $e_2 = y_2 - \hat{y}_2 \to -\hat{y}_2$. Let

$$
\mathbf{e}_{2,N} = \{e_2(k-N), \ldots, e_2(k-1)\}
$$

be the collection of $N$ residuals acquired when $y_2$ had no artifacts. Let $\bar{e}_2$ denote the arithmetic mean of the residuals in $\mathbf{e}_{2,N}$. Assume further that $e_2(k-i) \sim N(\bar{e}_2, \sigma^2)$ $\forall i = 1, \ldots, N$. The proposed test for artifact detection is:

$$
\mathcal{H}_0 : e_2(k) = \bar{e}_2
$$

$$
\mathcal{H}_1 : e_2(k) < \bar{e}_2.
$$

If at the sampling time $k$ the null hypothesis is rejected, then we consider $y_2(k)$ corrupted by artifacts. The alternative hypothesis is one-sided because all artifact sources tend to decrease $e_2(k)$. $\mathcal{H}_0$ is rejected at a confidence level $\alpha = 0.01$ if:

$$
\frac{e_2(k) - \bar{e}_2}{\sigma} < \Phi(\alpha) = -2.33
$$

where $\Phi(\alpha)$ is the cumulative distribution function of a standardized normal variable. If $\mathcal{H}_0$ is not rejected, then $e_2(k)$ updates the vector of residuals in Eq. (2.31). Otherwise the same vector is used for testing the residual $e_2(k+1)$. 
2.5 Implementation

We set $\sigma = 0.1$ in Eq. (2.34) on the basis of off-line tests. Such a test is described in Fig. 2.7. We used a data set collected during a clinical study, which was aimed at comparing endtidal concentration control versus manual control (Sieber et al., 2000). The first plot from above depicts endtidal concentrations and reference values during closed-loop (first part) control and during manual adjustment (second part) of the vaporizer by the anesthesiologist. The second plot depicts the residuals $e_2(k)$ together with the lower bound for acceptance defined in Eq. (2.34). Finally, in the third plot the vaporizer settings of the experiment which were used as input sequence for the model in Eqs (2.12,2.13) are plotted. Three periods where endtidal concentration measurements had artifacts can be recognized.

Figure 2.7: In the upper plot, endtidal concentration reference signal (— — —) and measurements (——) are plotted during closed (first half) and open-loop (second half) control. In the middle plot, the error residuals $e_2 = y_2 - \hat{y}_2$ (— + +) are plotted together with the lower bound for artifact detection. In the lower plot the vaporizer settings are depicted. All artifact episodes were properly detected.
at roughly $t = 28$ min, $t = 36-39$ min and $t = 156$ min. The first and last correspond to calibration of the measuring device whereas the second corresponds to a 3 min disconnection of the sampling line. Figure 2.7 shows that all artifacts were correctly identified.

The artifacts in BIS arising from the corruption of EEG with EMG are unlikely to occur since the patients receive high doses of muscle relaxants during the study. In all other cases such as low electrode impedance or accidental disconnection of the electrodes, we use the Signal Quality Index (SQI) as a basis for the detection. The SQI is an auxiliary value delivered by the BIS monitor at each sampling time. It is expressed as a percentage value, with 100% denoting a high quality measurement. Together with the staff from Aspect Medical System, we decided that BIS is unacceptably corrupted by artifacts when SQI < 20.

During artifacts the reliability of the system is guaranteed if the controller delivers meaningful input actions. The following decision rules were adopted (see Fig. 1.7):

1. if $y_2$ has artifacts, then we set $e_2 \equiv 0$ and the input of $P_1$ becomes $\tilde{y}_2$ instead of $y_2$. During this phase the closed-loop system is equivalent to a single IMC loop controlling BIS;

2. if $y_1$ has artifacts, then we set $e_1 \equiv 0$. In this case just the slave controller remains active;

3. when both $y_2$ and $y_1$ have artifacts, $e_2 \equiv 0$ and $e_1 \equiv 0$. In this case the system will operate in open-loop, which is the only option when there is no measurement available.

Let us examine in more detail the dynamics of the system in the presence of artifacts. Specifically, assume that artifacts occur in the BIS and/or endtidal concentration measurements at the sampling time $\tilde{k}$. Suppose further that no artifacts occurred before that, which implies that for $k < \tilde{k}$, $e_1(k) \neq 0$ and $e_2(k) \neq 0$. Setting $e_1 \equiv 0$ and/or $e_2 \equiv 0$ can be regarded as a set point change in the master and/or slave controller. Since both $Q_1$ and $Q_2$ are strictly proper, this procedure does not result in discontinuities of the control action. Let us assume the worst case situation where artifacts persist both in $y_1$ and $y_2$ for $k \geq \tilde{k}$. The controller will start an administration
profile which ultimately converges to a constant, safe vaporizer setting. This steady-state value is the input which would nominally result in a BIS equal to \( y_{1,ref} \) for the average subject in the population. It can be calculated by first inverting Eq. (2.7) to obtain the corresponding concentration at the effect compartment:

\[
x_{1,r} = EC_{50} \left( \frac{100 - y_{1,ref}}{y_{1,ref}} \right)^{\frac{1}{\gamma}}. \tag{2.35}
\]

Then from Eqs (2.14,2.5) we obtain desired vaporizer setting as:

\[
u_r = \left[ Q_0 - \Delta Q \left( 1 + \frac{V_1}{f_R (VT - \Delta)} \frac{k_{12} k_{20}}{k_{21} + k_{20}} \right) + \frac{V_1}{Q_0} \frac{k_{12} k_{20}}{k_{21} + k_{20}} \right] x_{1,r}
\]

\[
\tag{2.36}
\]

For a typical anesthetic procedure with \( f_R = 10 \) [1/min], \( VT = 0.6 \) [l], \( \Delta = 0.15 \) [l] \( Q_0 = 1 \) [l/min], \( \Delta Q = 0.2 \) [l/min] and \( y_{1,ref} = 50 \) and for the typical subject of the population we obtain from the above expression \( u_r = 0.71 \) [%].

### 2.6 Test of the controller

Two clinical tests of the BIS controller were already presented in chapter 1. We showed that the controller is able to target and maintain a desired level of unconsciousness assessed by BIS. In this section we report and discuss two particular cases showing the performance of the artifact detection system and the controller behaviour with a patient who exhibited tolerance to isoflurane. Further, we show the prediction accuracy of the PK models during closed-loop experiments. The details concerning the admission criteria to the studies and the premedication taken by the subjects were reported in chapter 1. The clinical study shown in Fig. 2.8 depicts an abnormal patient's behaviour that was correctly handled by the controller. A 60 years old man undergoing craniotomy was enrolled for the study. Figure 2.8 depicts the BIS and MAP signals during the operation, together with the input at the vaporizer. Blood pressure was measured non invasively with a pressure cuff. Automatic control was active during the whole period considered. During the initial period up to \( t = 205 \) min, the subject exhibited a vivid tolerance to isoflurane. Precisely, BIS values fluctuated around
Figure 2.8: In the upper plot BIS and BIS reference values during closed-loop are represented. In the middle plot systolic, mean and diastolic arterial pressures acquired with a blood pressure cuff are represented. In the lower plot the vaporizer settings determined by the closed-loop controller are plotted. The controller was active during the whole period represented in the figure.

50 while BIS reference values were set to 40. The input at the vaporizer kept increasing during that phase. At roughly $t = 206$ min a bolus dose of alfentanil was administered to compensate for a sharp increase of blood pressure, which was regarded as a sign of inadequate analgesia. Shortly after, BIS values dropped to around 10. It is not certain, even though highly probable, that such drop was a consequence of the bolus dose of analgesic. Let us recall that the effect of alfentanil on BIS was not completely ruled out by the data collected from the study on volunteers. The controller promptly reacted to the sudden drop in BIS values by reducing the vaporizer setting almost to 0. At $t = 251$ min the BIS reference value was increased to 60. Symmetrically to the initial phase, the patient remained unresponsive to
changes in the vaporizer settings.

Figure 2.9: In the upper plot BIS and BIS reference values during closed-loop are represented. In the middle plot endtidal concentration references and measurements are depicted. In the lower plot the vaporizer settings are plotted. The solid line in the lower plot indicates the period where the controller was active.

Figure 2.9 illustrates the controller’s behaviour during occurrence of an artifact in BIS measurements. The case of a 63 years old female undergoing hernia removal is considered. Figure 2.9 represents the operative profile of BIS, endtidal concentrations and vaporizer settings. At $t = 159$ min roughly BIS electrodes were disconnected accidentally without anybody in the operating room noticing the fact. During this transient the master controller operates without feedback signal. As a result, the endtidal concentration reference signal did converge to a constant value which is capable of achieving the specified BIS reference in the average patient. Such value is approximately 0.6%, as calculated from the pooled PD relationship represented in Fig. 2.5. When artifacts disappeared, the master controller was
switched on again by the supervisory system. Consequently, new endtidal concentration references were computed on the basis of BIS values.

\[\text{Figure 2.10: In the upper plot measured (——) and predicted (———) isoflurane concentrations whereas in the lower plot measured and predicted endtidal concentrations are represented.}\]

In the cases where isoflurane was administered through the control platform, the states of the parallel model $P_2$ can be regarded as estimates of the corresponding measurements. Figure 2.10 shows excellent agreement between predicted inspired and endtidal concentrations and their corresponding model predictions. It is worth noticing that the plot shows comparisons at different fresh gas flow rates. Precisely at $t = 130$ min the fresh gas flow was decreased from $Q_0 = 2 \text{l/min}$ to $Q_0 = 1 \text{l/min}$. The predictions as well as the endtidal controller performance remained accurate during the change as a result of the model update. This confirms that the PK model provides an accurate description not only for the volunteers but also for the patients during closed-loop control.
Chapter 3

Feedback Control of Analgesia
Foreword

In chapter 1 we compared two approaches for the closed-loop administration of volatile hypnotics: either to regulate Mean Arterial Pressure (MAP) or to regulate Bispectral Index (BIS). In chapter 2 we thoroughly investigated the second approach, both from a control theory and a clinical perspective. From both treatises one can conclude that BIS may be used with advantage as a guide for hypnotic administration.

What do we do with MAP now?

MAP is not only an indirect indicator to assess depth of anesthesia or adequate perfusion to internal organs. The signal itself and its fluctuations in correspondence to surgical stimulation are signs of responsiveness of the autonomic system. The reactions of the autonomic system must be minimized for the patient’s sake and to improve the operating conditions. Analgesic drugs may be used with advantage to achieve this goal.

In the following chapter a new paradigm for the closed-loop administration of analgesics during general anesthesia is presented. The manipulated variable in the control system is the infusion rate of the opiate alfentanil, administered intravenously through a Computer Controlled Infusion Pump (CCIP). The outputs to be controlled are the patient’s Mean Arterial Pressure (MAP) and the drug concentration in the plasma. Maintaining MAP within appropriate ranges improves the operating conditions for surgical intervention and provides optimal treatment of the patient’s reactions to surgical stimuli. Maintaining plasma drug concentrations within ranges specified by the operator enables anesthesiologists to titrate analgesic administration to qualitative clinical end-points of insufficient analgesia. MAP is acquired both invasively and non-invasively through a catheter cannula and a blood
pressure cuff, respectively. Since plasma drug concentrations cannot be measured on-line, they are estimated via a pharmacokinetic (PK) model on the basis of the infusion profile. An explicit Model Predictive Controller (MPC) was designed to achieve the above mentioned objectives. An upper constraint on predicted drug concentrations was imposed to avoid overdosing, whereas constraints on the MAP were introduced to trigger a prompt controller reaction during hypertensive and hypotensive periods. Artifacts in the MAP measurements are rejected to prevent harmful misbehavior of the controller. Finally, the results of the application of the controller to 6 patients are presented and discussed.

This chapter can be found with minor modifications as a publication in the scientific literature as:

3.1 Introduction

3.1.1 Intraoperative analgesic administration

Opiates are used for intraoperative and postoperative pain treatment. In the postoperative setting, the drug infusion rate is adjusted according to the patient's pain level. With Patient Controlled Analgesia (PCA), the patient can regulate the administration of opiates without supervision of the medical staff (Scherpereel, 1991; Liu and Northrop, 1990; Johnson and Luscombe, 1992).

The intraoperative administration of opiates is not directly related to pain treatment, since no specific measure of pain are available when the subject is unconscious (Habibi and Coursin, 1996). The International Association for the Study of Pain defines pain as an 'unpleasant sensory and emotional experience associated with actual or potential tissue damage'. Consequently, it may even be improper to speak about "pain" during general anesthesia when the patient experiences unconsciousness (Petersen-Felix et al., 1998).

Opiates are infused because they decrease autonomic stress reactions to surgical stimulation (Ausems et al., 1988; Kaplan, 1993), such as MAP and Heart Rate (HR) increases. These reactions must be minimized during surgery (Prys-Roberts, 1987).

For several reasons a SISO controller for MAP with opiates is clinically not feasible. Firstly, opiates are generally considered to be hemodynamically stable, that is increasing opiate concentrations in the plasma generally do not decrease MAP. If the MAP is elevated because of pain, opiates generally decrease MAP. Secondly, it was shown that even high doeses of opiates may not be able to suppress MAP reactions to noxious stimulation completely (Wynands et al., 1984; Hynynen et al., 1986; Phibin et al., 1990). Consequently, a control system which purely adjusts the opiate infusion rate on the basis of the patient's MAP may lead to prolonged respiratory depression at the end of surgery (Shafer and Varel, 1991). Thirdly, MAP can be low independently from opiate concentrations, for instance when volatile hypnotic or vasoactive drugs are used. In this case the controller may lead to underdosing.
3.1 Introduction

Several open- and closed-loop approaches have been investigated to improve the intraoperative administration of analgesics. Ausems and colleagues titrated opiate infusion to several clinical endpoints such as MAP and Heart Rate (HR), somatic responses and autonomic signs of inadequate anesthesia such as sweating and lacrimation (Ausems et al., 1986). In their clinical protocol, the infusion rate of alfentanil was gradually decreased in the absence of signs of inadequate analgesia as a remedy to prevent overdosing.

Schwilden and Stoeckel tested a closed-loop controller which administers alfentanil to maintain the patient’s Median Frequency (MF) of the electroencephalogram (EEG) at 2-4 Hz (Schwilden and Stoeckel, 1993). Despite the adequate performance of the control system, it is questionable to look at the MF of EEG as the clinical end-point for analgesic drugs. Further, if used in combination with analgesics, hypnotics compromise the reliability of MF by inducing burst suppression episodes in the EEG (Rampil, 1998). Moreover, from clinical data it is not clear whether and how noxious stimuli affect the EEG (Rampil and Laster, 1992; Kochs et al., 1994).

Carregal and colleagues tested a closed-loop fuzzy controller for MAP and HR with alfentanil during gynecological surgery (Carregal et al., 2000). The light level of stimulation for such surgical procedures and the slow sampling rate of the controller do not allow to extrapolate the reported performance to periods of intense stimulation and more invasive surgical procedures.

Both studies are encouraging because they confirm the possibility of achieving good hemodynamic control with opiates. They also suggest that an optimal closed-loop system aiming at the regulation of MAP with opiates must include a means to minimize the drug consumption and must offer some degree of freedom to adjust the infusion rate based on other qualitative signs of inadequate analgesia. None of these issues have been embedded in a control system so far.

3.1.2 Goal of this study

In the feedback system for the administration of analgesic drugs that we present in this chapter, the patient’s MAP and the predicted drug concentrations in the plasma are the outputs to be controlled. We designed the control algorithm to achieve multiple clinical objectives:
• during stable periods where both outputs lie within constraints, the control system must adjust the infusion rate mainly to keep MAP around a reference value specified by the anesthesiologist;

• the controller must maintain plasma drug concentrations around a reference value specified by the anesthesiologist as a secondary objective beyond MAP regulation;

• the controller must react promptly when output constraints are violated. Also, it must treat constraints violations with different aggressiveness, since not all violations have the same clinical severity.

Alfentanil was chosen as the opiate for this study because of its relatively fast blood-brain equilibration and the moderate pharmacokinetic (PK) variability (Shafer and Varvel, 1991).

In this chapter we describe the design principles and the clinical validation of the control system for analgesic administration. First, we outline the model used for control. It consists of a pharmacokinetic (PK) model adapted from the literature and an approximate pharmacodynamic (PD) model whose parameters were defined on the basis of anesthesiologists' experience. Second, the control algorithm is described. It consists of an explicit Model Predictive Controller (MPC), which is the only control strategy capable of handling both multiple control objectives and constraints prioritization in a consistent way. In particular, we discuss the choice of the optimization weights, the weights on the output constraints and the horizons lengths and their influence on the closed-loop performance. Third, we present an algorithm for the rejection of artifacts in the MAP signal, which was added to make the controller applicable in the operating room (OR). Fourth, the closed-loop performance of the controller, when applied during general surgery on humans, is presented and discussed, together with some suggestions for future research.

We designed a novel feedback paradigm for the intraoperative administration of analgesic drugs. To the author's best knowledge the one described here is the first model-based closed-loop control system to regulate MAP with opiates.
3.2 Modeling

The linear three-compartment mammillary PK model depicted in Fig. 3.1 was adopted to describe the distribution characteristics of alfentanil. A

![Diagram of three compartment PK model for the distribution of alfentanil.](image)

Figure 3.1: Three compartment PK model for the distribution of alfentanil. $k_{e0}$ [min$^{-1}$] is the equilibration constant of the effect compartment.

A mass balance equation for the central compartment gives:

$$\frac{dC_1}{dt} = \sum_{j=2}^{3} k_{1j}(C_j - C_1) - k_{10}C_1 + \frac{\rho}{kV_1}u$$

(3.1)

where $C_1$ [ng/ml] and $C_j$ [ng/ml] represent plasma and auxiliary compartment concentrations, respectively. $V_1$ [ml] is the volume of the central compartment, $k_{1j}$ [min$^{-1}$] ($j = 2, 3$) are the drug transfer rates between the central and the auxiliary compartments, $k_{10}$ [min$^{-1}$] is the elimination rate, $\rho = 5 \cdot 10^5$ [ng/ml] is the alfentanil concentration in the syringe, $k = 60$ [min/h] is a normalization constant and $u$ [ml/h] is the infusion rate. The concentrations in the auxiliary compartments are described by:

$$\frac{dC_j}{dt} = k_{j1}(C_1 - C_j) \quad j = 2, 3.$$  

(3.2)

Note that Eqs (3.2) and (3.1) imply that, for a constant infusion rate, the steady-state concentrations in all the compartments are equal.
The prediction performances of the following published models for alfentanil were compared to select the best candidate for control design: Scott (Scott and Stanski, 1987), Scott weight-adjusted, Maitre (Maitre et al., 1987), Hudson (Hudson et al., 1991) and Shafer. The parameters of Scott’s weight-adjusted and Shafer’s models were obtained from the source code of the software STANPUMP\(^1\). As a measure of performance, we computed the prediction errors between model estimates and measured alfentanil concentrations collected during the volunteer study, which was already described in chapter 2. In that study that 20 young healthy volunteers were anesthetized with isoflurane for approximately 5 h. Alfentanil was continuously infused during the study to achieve and maintain constant levels of predicted plasma concentration between 25 ng/ml and 400 ng/ml. Target controlled infusion (TCI) algorithms were implemented using STANPUMP\(^1\) software with Shafer’s PK model for alfentanil. Approximately 20 alfentanil samples were taken per subject during transient and steady-state phases.

According to the standard techniques to evaluate prediction performance of CCIP (Varvel et al., 1992), we calculated for each drug sample the percentage Prediction Error ($PE_{ij}$) as:

$$PE_{ij} = \frac{C_{mij} - C_{p_{ij}}}{C_{p_{ij}}} \cdot 100$$  \hspace{1cm} (3.3)

where $C_{p_{ij}}$ and $C_{m_{ij}}$ represent the predicted and measured alfentanil concentrations at the $j^{th}$ sample for the $i^{th}$ subject. Additionally, we computed the Median Prediction Error ($MDPE_{i}$) and the Median Absolute Prediction Error ($MDAPE_{i}$) as:

$$MDPE_{i} = \text{median}\{PE_{ij}, j = 1, \ldots, N_{i}\}$$  \hspace{1cm} (3.4)

and

$$MDAPE_{i} = \text{median}\{|PE_{ij}|, j = 1, \ldots, N_{i}\}$$  \hspace{1cm} (3.5)

respectively. In Eqs (3.4) and (3.5) $N_{i}$ is the number of samples for subject $i$. $MDPE_{i}$ is an index for the bias of the model for a particular subject, whereas $MDAPE_{i}$ is an index for the dispersion of the model residuals. Finally, we computed $WOBBLE_{i}$ as:

$$WOBBLE_{i} = \text{median}\{|PE_{ij} - MDPE_{i}|, j = 1, \ldots, N_{i}\}$$  \hspace{1cm} (3.6)

\(^1\)STANPUMP is freely available from the author, Steven L. Shafer, M.D., Anesthesiology Service (112A), PAVAMC, 3801 Miranda Ave, Palo Alto, CA 94304.
which represents a bias free measure of the variability of $PE_{ij}$ in the $i^{th}$ individual. The prediction accuracy of Maitre’s and Hudson’s models was remarkably lower compared to the other models. No significant differences in all the performance parameters were found between Scott’s and Scott’s weight-adjusted models. Therefore we excluded Maitre’s, Hudson’s and Scott’s models from further discussion. Figure 3.2 shows the profile of predicted and measured plasma concentrations for a subject in the study. The step behaviour of plasma concentrations predicted by Shafer’s model follows from the fact that this model was chosen for the TCI algorithm (Bailey and Shafer, 1991). Shafer’s model is strongly overpredicting plasma concentrations, as confirmed by comparing the average $MDPE$ among the subjects for the two different models: Scott weight-adjusted (-14.29) and Shafer (-
31.49. No substantial differences were observed in the average MADPE or in the average WOBBLE for the different models. Despite the bias, Shafer’s model provides a more uniform performance among the population, as deducible by visual comparison of the boxplots represented in Fig. 3.3 for Shafer’s and Scott’s weight-adjusted models. We decided to adopt Shafer’s weight-adjusted model as the PK model in the MPC scheme. To compensate for the prediction bias we re-estimated the volume of the central compartment. This heuristic procedure reduced the prediction bias without significantly deteriorating the other performance parameters. The volume of the central compartment in the PK model depends on the subject’s Body Surface Area.

![Boxplots of the Prediction Errors (PEij) for Shafer's (left) and Scott's weight-adjusted (right) models and every subject in the study. Despite the bias, the variability of the Prediction Errors in Shafer's model is more uniform among the population of subjects.](image)
3.2 Modeling (BSA) through the following relationship:

\[ V_1 = c \cdot BSA. \]

where \( c = 0.825 \) in the published set of parameters. BSA is computed as

\[ BSA = 0.007184 \cdot w^{0.425} \cdot h^{0.725} \]

where \( w \) [kg] and \( h \) [cm] represent the subject’s weight and height, respectively. We minimized the average MDPE among the subjects with respect to the \( c \) parameter in Eq. (3.7), obtaining as an optimal value \( c_{opt} = 1.1028 \). The fact that \( c_{opt} > 0.825 \) was to be expected since larger volumes decrease the concentrations predicted by the model. Figure 3.4 depicts MDPE, MDAPE and WOBBLE with increasing values of \( c \). It is interesting to notice that \( c = 1.1028 \) is also close to the value minimizing the average MDAPE and that WOBBLE is just slightly worsened relative to the original value.

There is no published PD model quantifying the effects of alfentanil on MAP. Consequently, an approximate PD model was tuned to reproduce the anesthesiologists’ clinical experience. An effect compartment was linked to the central compartment, as depicted in Fig. 3.1 (Schnider et al., 1994). The concentrations at the effect site \( C_e \) [ng/ml] are related to plasma concentrations by the following equation:

\[ \frac{dC_e}{dt} = k_{e0} (C_1 - C_e) \]

where \( k_{e0} \) [min\(^{-1}\)] is the equilibration constant at the effect site. The value for \( k_{e0} \) in Eq. (3.9) was calculated in order to reproduce an observed time to peak effect on MAP after a bolus injection of alfentanil of \( t_{peak} = 1.5 \) min. In the estimation, we adopted Shafer’s PK model with \( c = c_{opt} \) and we assumed an average subject with \( w=70 \) kg and \( h=180 \) cm. We obtained \( k_{e0} = 0.4 \) [min\(^{-1}\)]. Since the MPC algorithm requires a linear model, we assumed a linear relationship between MAP and effect site concentration variations with a gain of \( k = -0.0881 \) [mmHg/(ng/ml)]. The gain value was derived through linearization of an approximate PD relationship postulated by anesthesiologists. Even though - as we discussed in the introduction - opioids may not affect MAP, the sign of the gain guarantees that the infusion rate will decrease when MAP is too low or increase when MAP is too high.

Table 3.1 summarizes the PK and PD parameters of the model used in the MPC control algorithm.
3.3 Control design

Figure 3.5 depicts the block diagram adopted for the closed-loop administration of alfentanil, where $P$ represents the patient, $M$ represents Shafer’s adjusted PK model, $C$ is the MPC controller and $K$ represents the observer, where artifacts are rejected according to the algorithm described further. $M$ computes predictions of the drug concentration in the plasma $y_1$ from the infusion rates of the syringe $u$. As mentioned earlier, the dynamic system $M$ has two roles: on one hand, it provides anesthesiologists with a patient’s weight and height adjusted estimate of the drug levels. On the other hand, it provides the MPC controller with the second output measure which must be regulated during closed-loop administration. $y_{1,ref}$ represents plasma concentration references. $\hat{x}$ represents the observer states, $y_2$ and $y_{2,ref}$ are MAP measurements and references, respectively.
### 3.3 Control design

#### Parameter Value

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_i$</td>
<td>1.1028 BSA [l]</td>
</tr>
<tr>
<td>$k_{12}$</td>
<td>0.515 [min$^{-1}$]</td>
</tr>
<tr>
<td>$k_{21}$</td>
<td>0.142 [min$^{-1}$]</td>
</tr>
<tr>
<td>$k_{13}$</td>
<td>0.231 [min$^{-1}$]</td>
</tr>
<tr>
<td>$k_{31}$</td>
<td>0.0185 [min$^{-1}$]</td>
</tr>
<tr>
<td>$k_{e0}$</td>
<td>0.4 [min$^{-1}$]</td>
</tr>
<tr>
<td>$k$</td>
<td>-0.0881 [mmHg/(ng/ml)]</td>
</tr>
</tbody>
</table>

Table 3.1: PK and PD parameters in the MPC controller.

![Block diagram of the explicit MPC controller.](image)

Figure 3.5: Block diagram of the explicit MPC controller.

#### 3.3.1 Controller tuning

At every discrete time step $k$, the MPC algorithm computes the $m$ following input actions \{u(k|k), \ldots, u(k + m - 1|k)\} which minimize the objective
Figure 3.6: Schematic diagram of the MPC optimization problem in Eq. (3.10).

The quadratic objective criterion expressed in Eq. (3.10) aims at minimizing both control errors $\epsilon_j = y_{j,ref} - y_j$ as well as inputs $u$, input rates $\Delta u$ and constraint violation $\epsilon$ for the future $p$ steps ahead. Note that the control error at the generic future time step $k + i$ is computed as deviation of the output reference from the predicted output value. Precisely, $\epsilon_j(k+i) = y_{j,ref} - y_j(k+i)$. The control actions computed by the MPC algorithm are implemented in a so-called receding horizon policy. Namely, at every time step $k$ just the first of the $m$ computed
3.3 Control design

input actions is implemented. At the end of the sampling time, a new measurement updates the states of the observer and the optimization in Eq. (3.10) is repeated.

In Eq. (3.10) \( p \) and \( m \) are usually defined prediction and control horizons, respectively, whereas \( \{w^{\Delta u}, w^n, w^{y_1}, w^{y_2}\} \) are the weights on input increments, input and outputs respectively. \( \epsilon \) is a ‘slack’ variable introduced to guarantee feasibility, whereas \( \rho \) is the weight on the output constraints in the optimization algorithm (Garcia et al., 1989). \( \{b_{1,\text{min}}, b_{1,\text{max}}, b_{2,\text{min}}, b_{2,\text{max}}\} \) represent tolerance weights for constraint violation. Precisely, the higher the parameter corresponding to a certain constraint, the less aggressive will the controller be when such a constraint is violated. In Eq. (3.11) we have \( u_{\text{min}} = 0 \) and \( u_{\text{max}} = 1000 \text{ ml/h} \).

Tuning of the MPC controller in Eq. (3.10) requires to specify the horizon lengths \( p \) and \( m \), the optimization weights \( \{w^{\Delta u}, w^n, w^{y_1}, w^{y_2}, \rho\} \) as well as the output constraints \( \{y_{1,\text{max}}, y_{1,\text{min}}, y_{2,\text{max}}, y_{2,\text{min}}\} \). The tolerance weights \( \{b_{1,\text{min}}, b_{1,\text{max}}, b_{2,\text{min}}, b_{2,\text{max}}\} \) and the internal model to predict the future output estimates must also be specified. The rationale behind the choice of the model was discussed in the previous section.

In order to better understand the role of the weights \( \{w^{\Delta u}, w^n, w^{y_1}, w^{y_2}, \rho\} \), let us observe that the MPC controller computes the infusion rate to maintain both \( y_1 \) and \( y_2 \) at their target level, despite MAP reactions induced by surgical stimulation. Since the controller uses one input to regulate two outputs, the infusion rate will be computed by the MPC algorithm to realize a dynamic trade-off between minimizing the control error \( \epsilon = y_{\text{ref}} - y \) for the first and the second output, respectively. The aggressiveness of the controller to minimize \( y_{1,\text{ref}} - y_1 \) rather than \( y_{2,\text{ref}} - y_2 \) or the other way round is determined by the ratio of the two output weights \( w^{y_1} \) and \( w^{y_2} \). In the limiting case where \( w^{y_1}/w^{y_2} \to 0 \), the control strategy reduces to a simple SISO controller for MAP. Conversely, if \( w^{y_1}/w^{y_2} \to \infty \) the control algorithm results in open-loop infusion policies to target plasma concentrations (Gentilini et al., 2000; Bailey and Shafer, 1991). Tuning of the optimization weights was performed to achieve two specific clinical goals. First, the controller should not aim at tightly maintaining the reference value \( y_{2,\text{ref}} \) for MAP. Rather, it should react moderately if \( y_2 \) lies within constraints and more aggressively if the constraints are hit. The same prompt controller’s reaction is desired if predicted concentrations hit their
respective constraints. As a second priority, the anesthesiologist must have a degree of freedom to adjust the infusion rate during automatic control to other qualitative indicators of insufficient analgesia. That is, the controller should react moderately to changes in $y_{1,\text{ref}}$ during stable periods where $y_2$ lies within the constraints. To achieve the above discussed goals, we set $w^{y_1} < w^{y_2} < \rho_e$. Particularly, we adopted $w^u = 10^{-4}$, $w^{\Delta u} = 0.5$, $w^{y_1} = 0.004$, $w^{y_2} = 2$, $\rho_e = 2 \cdot 10^4$.

The output constraints for both MAP and predicted plasma concentration are chosen by the anesthesiologist before induction of anesthesia according to the patient’s cardiovascular conditions and the type of surgical procedure.

How the choice of both $m$ and $p$ horizons affects the complexity of the control algorithm will be outlined in the following section.

### 3.3.2 Explicit MPC Controller

Even though the long sampling time in the real-time platform ($T_s = 5$ s) would allow to implement the optimization problem in Eq. (3.10) on-line, we chose the explicit form of the MPC algorithm. In this formulation, Eq. (3.10) is resolved as a piece-wise affine control algorithm, which enabled anesthesiologists to visualize more directly the effects of a specific set of weights on the controller’s performance. Finally, it contributed significantly to the acceptance of the control algorithm in the operating room.

In the explicit MPC formulation the update of the controller’s action $\Delta u(k) \triangleq u(k) - u(k - 1)$ is an affine function of the observer states $\hat{x}(k)$, the input at the previous time step $u(k - 1)$ and the reference signals $y_{1,\text{ref}}(k)$ and $y_{2,\text{ref}}(k)$. As mentioned earlier, the explicit MPC controller must be considered as an equivalent formulation of the optimization problem in Eq. (3.10). The interested reader can find the theoretical details of such equivalence in the literature (Bemporad et al., 2000). Let us denote as $\theta(k) \triangleq [\hat{x}(k)^T, u(k - 1), y_{1,\text{ref}}(k), y_{2,\text{ref}}(k)]^T$ the controller’s states. First, the active control region is identified. This is defined via the index $i$ such that the inequalities

$$H_i \theta(k) \leq K_i \quad i = 1, \ldots, n_R$$

hold, where $n_R$ is the number of regions in which the explicit MPC con-
controller partitions the space $\Theta \subset \mathbb{R}^8$ in which $\theta$ may vary. Eq. (3.16) states that $\theta$ belongs to the polyhedral region defined by the matrices $\{H_i, K_i\}$. Subsequently, the update of the infusion rate is computed as

$$\Delta u(k) = F_i \theta + G_i.$$  

where the matrices $\{F_i, G_i\}$ define the piece-wise affine control action in region $i$. In the worst case situation, $n_R$ may increase exponentially with $p$ and $m$ (Bemporad et al., 2000). We chose $p = 10$ and $m = 3$ to minimize the controller’s complexity while guaranteeing adequate performance, obtaining $n_R = 127$.

![Figure 3.7](image.png)

Figure 3.7: State-space partition of the MPC controller for two different sets of output weights. We set the observer states $\hat{x}(k)$ to represent a constant concentration in all the compartments of $C = 200$ ng/ml and a constant MAP=90 mmHg. Further, we set $u(k - 1) = 3.7$ ml/h, which would result into a steady-state concentration of $C = 200$ ng/ml. On the x- and y-axis $y_1, \text{ref}$ and $y_2, \text{ref}$ are represented, respectively. In the upper and lower plot, regions for $r = 150$ and $r = 10^2$ are represented.
Figure 3.8: For a detailed description of the content of the plot, refer to the caption of Fig. 3.7. In the upper and lower plot, regions for \( r = 150 \) and \( r = 10^{-3} \) are represented.

An example is represented in Fig. 3.7, where the partition of the space \( \Theta \subset \mathbb{R}^8 \) of the explicit MPC algorithm for two different sets of output weights is depicted. In both plots, the same set of weights for the input, the output constraints and input increments was considered. Every region defined according to Eq. (3.16) is represented with a different gray-scale. In order to be able to draw the regions in a 2-dimensional space, we fixed the first six elements of \( \theta \) to constant values. On the x- and y-axis, different values for the output references \( y_{1,\text{ref}} \) and \( y_{2,\text{ref}} \) inside the output ranges are considered, respectively. In the upper plot, we chose output weights such that \( r = \frac{w^{y_2}}{w^{y_1}} = 150 \) whereas in the lower plot we set \( r = 3000 \). The different choices of the output weights affect both the affine control action in Eq. (3.16) as well as the topology of the regions partition in the state space. As an example, let us consider the point \( P_1 \) depicted in Fig. 3.7 such that \( y_{1,\text{ref}} = 120 \text{ ng/ml} \) and \( y_{2,\text{ref}} = 80 \text{ mmHg} \). Since \( y_{1,\text{ref}} < y_1 \), the controller
would decrease the infusion rate to track predicted plasma concentrations. However, since \( y_{2,ref} < y_2 \), the controller would also increase the infusion rate to lower MAP. Let us consider first the regions for \( r = 150 \). The final input actions computed with Eq. (3.16), which are optimal in the sense of Eq. (3.10) are \( \Delta u = [-3.04 - 0.69 \ 0]^{T} \). That is, for this particular choice of the output weights, the control error \( y_{1,ref} - y_1 \) dominates \( y_{2,ref} - y_2 \) in determining the future input actions at the point \( P_1 \). Not surprisingly, for \( r = 3000 \) we would obtain \( \Delta u = [14.88 12.29 9.98]^{T} \). That is, MAP deviations from the reference value dominate in this case. Also, let us consider the point \( P_2 \) for which \( y_{1,ref} = 240 \) ng/ml and \( y_{2,ref} = 80 \) mmHg. In this case, both control errors would lead the controller to increase the infusion rate. As a result of the higher ratio \( r \), the increments of the infusion rate are significantly higher for the second set of regions. Precisely, we have \( \Delta u = [18.24 15.36 12.77]^{T} \) against \( \Delta u = [9.52 6.58 4.08]^{T} \), which were computed for the first set of regions. Moreover, let us notice that in the lower plot \( P_1 \) and \( P_2 \) belong to the same active region, unlike for the upper plot. This is generally true for the regions depicted in the lower plot. That is, once the control error \( y_{2,ref} - y_2 \) is fixed, there is just one affine control law which covers the state space regardless of the values for \( y_{1,ref} - y_1 \). This is a consequence of the higher \( r \) in the lower plot. This behaviour can also be justified by considering that for high \( r \) values the Single Input Multiple Output (SIMO) controller becomes a SISO controller for the output variable with the dominant weight. As a result, the active linear controller is uniquely determined by such output variable. Figure 3.8 depicts regions corresponding to a high weight for first output and supports this conjecture. In the lower plot, the regions computed for \( r = 10^{-3} \) and the same set of other optimization weights as for Fig. 3.7 are represented. In the upper plot, the same set of regions depicted in the upper plot of Fig. 3.7 are depicted for ease of comparison. Again, as a result of a higher weight for the first output, the regions are essentially defined by the values of \( y_{1,ref} - y_1 \) rather than \( y_{2,ref} - y_2 \).

We may conclude that the topology of partition in the state space is also affected by other factors such as the complexity of the optimization problem, the constraints on the output variables and the particular section of the state space considered in this example. However, Figures 3.7 and 3.8 lead us to consider the ratio of the two output weights \( r \) as a relevant factor determining the topology of the explicit MPC controller.
Figure 3.9 depicts the steady-state behaviour of the controller as a function of the ratio of the output weights $r$. On the x-axis, MAP deviations from the target values $\Delta y_2 = y_2 - y_{2,ref}$ are represented, whereas on the y-axis plasma concentration deviations $\Delta y_1 = y_1 - y_{1,ref}$ are represented. We obtained the curves depicted in Fig. 3.9 by computer simulation. The plot shows that if, during the closed-loop drug administration, the patient’s MAP stays permanently away from the reference value by $\Delta y_2$, then the controller will infuse to maintain plasma concentration such that $\Delta y_1 = \alpha \Delta y_2$, where $\alpha$ is the slope of the straight line corresponding to the particular set of weights in use. Not surprisingly, $\alpha$ increases with $r$. We chose $y_{1,ref} = 100$ ng/ml, $y_{1,max} = 400$ ng/ml, $y_{1,min} = 0$ ng/ml, and $y_{2,ref} = 80$ mmHg to simulate the steady-state controller’s behaviour depicted in Fig. 3.9. As a result of this particular choice, all the straight lines reach a lower and an upper asymptote at $\Delta y_{1,max} = -100$ ng/ml and $\Delta y_{1,max} = 300$ ng/ml, respectively. However, the same type of linear behaviour applies regardless of the specific values for $y_{1,ref}$ and $y_{2,ref}$.
3.3 Control design

3.3.3 Artifact tolerant controllers

Because measurement artifacts deteriorate the controller’s performance and can be harmful for the patient (Fukui and Masuzawa, 1989), an appropriate algorithm to detect and remove artifacts was designed. Unlike other applications where artifacts occur in exceptional cases, in anesthesia they are caused by routine manipulation of both the measuring devices and the patient (Reid and Kenny, 1987; Ruiz et al., 1993). In our application, where the blood pressure signal is acquired through the invasive method depicted in Fig. 3.10 there are several sources of artifacts. Firstly, they occur when the catheter line is flushed to prevent blood clots or whenever blood samples are taken. Secondly, they may result from calibration of the measuring device or involuntary movement of the catheter (Van Egmond et al., 1985). Our group proposed a theoretical framework for handling artifacts in observer-based control schemes (Frei, Bullinger, Gentilini, Glattfelder, Sieber and Zbinden, 2000; Frei, Kraus and Blanke, 1999; Frei, 2000). This approach was extended here to the case of MPC and complemented with an approach based on signal analysis techniques. Both approaches run in parallel during closed-loop drug administration. That is, MAP measurements are considered corrupted by artifacts when the first or the second method detects them.

![Figure 3.10: Invasive blood pressure measuring system. During normal functioning, the continuous blood pressure signal is acquired through the catheter inserted into the radial artery. To take a blood sample, the three-way valve must be rotated by 90° counterclockwise. To flush the system, the pigtail must be pulled. In both cases the transducer receives the input signal from the pressurized solution instead of the catheter.](image)

In order to describe the observer-based approach, let us consider the follow-
ing discrete-time state space model:

\[
\begin{bmatrix}
    x_c(k+1) \\
    n(k+1)
\end{bmatrix} =
\begin{bmatrix}
    A_c & 0 \\
    0 & 1
\end{bmatrix}
\begin{bmatrix}
    x_c(k) \\
    n(k)
\end{bmatrix} +
\begin{bmatrix}
    B_c \\
    0
\end{bmatrix} u(k) + w(k) \tag{3.18}
\]

\[
y(k) = C \begin{bmatrix}
    x_c(k+1) \\
    n(k+1)
\end{bmatrix} + v(k) \tag{3.19}
\]

where the states are the concentrations in the different compartments \(x_c(k)\) described by Eqs (3.1,3.2,3.9) and an additional state \(n(k)\) which was added to cope with MAP disturbances. Eqs (3.18,3.19) can be regarded as the discrete-time equivalent of the PK model introduced with Eqs (3.1,3.2,3.9) together with a disturbance model represented by the additional state \(n(k)\). The dynamics of \(n(k)\) are described by a pure integrator, which was sufficient to capture all the MAP disturbances triggered by clinical intervention. \(A_c\) and \(B_c\) are the discrete-time equivalents of Eqs (3.1,3.2,3.9). The outputs \(y(k)\) in Eq. (3.19) are plasma concentrations and MAP, respectively. We assumed that MAP can be regarded as the superposition of the effect site contribution and the additional state \(n(k)\). Summarizing, we have:

\[
C = \begin{bmatrix}
    1 & 0 & 0 & 0 & 0 \\
    0 & 0 & 0 & k & 1
\end{bmatrix} \tag{3.20}
\]

where \(k\) assumes the value reported in Tab. 3.1. \(w(k)\) and \(v(k)\) in Eqs (3.18,3.19) were modeled as white noise sequences with covariances:

\[
E(w(k)w^T(k)) = \begin{bmatrix}
    P_c & 0 \\
    0 & P_n
\end{bmatrix} \tag{3.21}
\]

\[
E(v(k)v^T(k)) = \begin{bmatrix}
    O_c & 0 \\
    0 & O_n
\end{bmatrix}. \tag{3.22}
\]

We chose \(P_c = 0.1\), \(P_n = 1\), \(O_c = 0.1\), \(O_n = 1\). A discrete-time observer was designed from Eqs (3.18,3.19) and Eqs (3.21,3.22) using the Kalman filter design methods. Artifacts in MAP lead to unreasonable estimates of the observer states. As a consequence, the controller’s performance would deteriorate and the patient’s safety would be put at risk. Therefore artifacts are rejected in the update equation of the observer states:

\[
\dot{x}(k+1|k) = A\hat{x}(k|k-1) + Bu(k) + Le(k)\hat{e}(k) \tag{3.23}
\]

\[
\dot{y}(k+1|k) = C\hat{x}(k+1|k) + Du(k) \tag{3.24}
\]
where $e(k) \triangleq y(k) - \hat{y}(k)$, $L$ is the innovation matrix and

$$
\psi(e(k)) = \begin{cases} 
1 & |y_2(k) - \hat{y}_2(k)| \leq b \\
\frac{2}{a + (|e(k)| - b)^2} & |y_2(k) - \hat{y}_2(k)| > b 
\end{cases}
$$

(3.25)

The idea behind Eqs (3.23,3.24) and Eq. (3.25) is to reject MAP measurements leading to outlying values of the residuals $e(k)$. The nonlinear mapping $\psi(e(k))$ is represented in Fig. 3.11. We can interpret Eq. (3.23) as follows: at every sampling time, the states of the observer are updated with the MAP value given by:

$$
y^*(k) = y(k) + \psi(e(k)) (y(k) - \hat{y}(k)).
$$

(3.26)

If no artifact occurs, $\psi \rightarrow 1$ and $y^*(k) \rightarrow y(k)$. When an artifact is detected ($\psi < 1$), the observer states are updated with a weighted average of the measurement $y(k)$ and the observer prediction $\hat{y}(k)$. In this sense $\psi(k) \triangleq$
\( \psi(e(k)) \) in Eq. (3.25) can be regarded as a measure of confidence of the MAP measurement at that particular sample time. The proposed approach does not consider the presence of artifacts as a dichotomous indicator. If the artifact detection criterion is made sharper (i.e. small MAP deviations are considered to be artifacts) important MAP transients due to painful stimulus may be missed. On the contrary, if the artifact detection is made looser, most artifacts may lead to improper controller reaction.

By choosing \( b = 7 \) mmHg and \( a = 20 \) in Eq. (3.25) as thresholds for the artifact detection one can suppress successfully artifacts resulting from flushing of the catheter and blood sampling. We did perform an off-line simulation of the artifact detection scheme with real MAP data obtained from a particular surgical procedure. Figure 3.12 shows the performance during such a validation. It is worth noticing that the artifacts occurring at \( t = 68 \) min and the \( t = 74 \) min resulting from calibration of the measuring device and flushing of the catheter respectively, were correctly detected. Moreover, the MAP increase due to increased surgical stimulation at \( t = 50 \) min was appropriately captured by the observer dynamics. Note that the effect of artifacts at \( t = 74 \) min on the closed-loop infusion rate is minimized but not completely suppressed, since the measures \( \hat{y}(k) \) still do contribute to \( y^*(k) \), according to Eq. (3.26). This is necessary to guarantee that \( \hat{y}(k) \rightarrow y(k) \) when the period of artifact is over.

The observer-based approach hinges upon the assumption that all MAP transients resulting from occurrence of artifacts lead to changes in the dynamics of the residuals \( e(k) \) which are markedly faster than the transients resulting from surgical manipulation or physiological disturbances. This assumption may be violated during periods where intense surgical stimulation occurs, such as during the intubation phase. Figure 3.13 reports an example from a clinical study where MAP increased by 25 mmHg at \( t = 113.3 \) min in one sampling time as a reaction to intubation. The artifact detection algorithm consisted exclusively of the observer-based method described before. As depicted in the figure, MAP measurements were considered corrupted by artifacts when they weren’t. Consequently, the controller did not increase the infusion rate significantly. The beneficial effects of higher concentrations of analgesics during the intubation phase could not be observed.

A complementary approach based on simultaneous analysis of Systolic (SBP) and Diastolic (DBP) Blood Pressure was added to compensate for the short-
3.3 Control design

Figure 3.12: Off-line observer validation with clinical MAP data. In the upper plot, predicted and reference alfentanil concentrations are depicted. In the second plot measured MAP (—) is plotted together with the reference value, upper and lower constraints. The dotted line (⋯) represents the values \( y^*(k) \) which are fed back to the MPC controller. In the last plot, the closed-loop infusion rate is depicted. MAP artifacts at \( t = 68 \) min and at \( t = 74 \) min were correctly captured.

comings of the observer-based approach. The method derives from observing that during blood sampling or flushing or calibration of the measurement device no heart pulse is detected. This is due to the fact that during such transients the transducer of the measuring system depicted in Fig. 3.10 is not receiving the input signal from the catheter placed in the artery. In the absence of pulse, SBP and DBP delivered by the monitor converge to MAP. Consequently, the Pressure Peak (PP) defined as \( \text{PP} = \text{SBP} - \text{DBP} \) tends to outlying values.

A moving average approach was used to detect MAP artifacts with the
PP method. At every sampling time $k$, the actual PP is compared with the average of the past $N$ valid PPs. If the actual value deviates from the calculated mean at most by $\pm \Delta PP$, the corresponding MAP value is accepted and fed back to the MPC algorithm. Moreover, the actual PP updates the vector of adequate PP values. If not, the MAP predicted by the observer is fed back both to the controller and to the observer. The moving average of PP values was adopted to accommodate for higher PP at higher SBP. In any case, no PP values higher than 100 mmHg and lower than 20 mmHg are accepted. If artifacts persist, the infusion rate of the controller would be determined by the MAP predicted by the model of the patient included in the MPC algorithm and not by the MAP value itself. Using the mere model prediction when artifacts occurs guarantees safe administration for two reasons. First, MAP predicted by the PK-PD model embedded in the MPC algorithm will always be decreased by alfentanil, since we assume $k < 0$. Second, the model considered describes MAP profiles of a sensitive

Figure 3.13: Example of an incorrect artifact detection. For a detailed description of the contents of each plot, refer to the caption of Fig. 3.12.
subject without painful stimulus. One may venture to say that under these considerations, the infusion rate will always start to decrease as long as an artifact occurs when $y_2 > y_{2\text{, ref}}$.

Figure 3.14 reports an on-line validation of the proposed algorithm during a clinical study. We chose $N=5$, $\Delta PP = 15$ mmHg. At $t = 256$ min and $t = 291$ min two blood samples were taken and the PP values during those transients fall outside the allowable range. In spite of the large MAP values displayed by the monitor, there is no harmful increase of the infusion rate by the controller.

Figure 3.14: On-line validation of the artifact rejection procedure based on the PP values. In the first plot from above SBP, MAP and DBP are represented. In the second plot PP (•••) are plotted together with the upper and lower acceptable value. In the last plot, the infusion rate computed by the controller is represented.
3.4 Test of the Controller

In this section we discuss the results of the clinical validation of the MAP controller. Patients with cerebral perfusion abnormalities, hypertension or coronary artery disease were excluded from the study. Written informed consent was obtained shortly before the premedication visit. The patients received a 7.5 mg tablet of midazolam orally 30 min prior to anesthesia as a premedication. ECG, Pulsoxymetry, BIS-electrodes, intravenous line were installed prior to induction. A 22 gauge Teflon catheter for invasive arterial pressure measurement was inserted in the radial artery of the non dominant hand of the patient. Unconsciousness was induced with bolus doses of propofol and maintained with isoflurane right after intubation. The muscle relaxant mivacurium was administered before intubation.

In all cases presented here, the infusion rate was maintained by the anesthesiologist at \( u = 120 \text{ ml/h} \) for approximately 1 min before intubation to provide the patient with a sufficient initial amount of analgesic. Then automatic control was started with \( y_{1,\text{ref}} = 100 \text{ ng/ml} \) and \( y_{2,\text{ref}} = 70 \text{ mmHg} \). The upper and lower limit for predicted plasma concentration were set to \( y_{1,\text{max}} = 400 \text{ ng/ml} \) and \( y_{1,\text{min}} = 0 \text{ ng/ml} \), respectively. Concerning MAP, we set \( y_{2,\text{max}} = 120 \text{ mmHg} \) and \( y_{2,\text{min}} = 60 \text{ mmHg} \), respectively. We set \( r = 500 \), which results in a steady-state slope \( \alpha = 10 \text{ [ng/ml/mmHg]} \), as depicted in Fig. 3.9.

In the first clinical validation examined, a 37 years old woman who was scheduled for lumbar hernia removal was enrolled for the study. The surgery lasted approximately 1 hr. Figure 3.15 shows the closed-loop control performance after the patient was intubated. At \( t = 130 \text{ min} \) the patient was moved into a supine position before entering the operating room. This stimulation increased MAP values by 30 mmHg in 2.5 min approximately. The controller increased the infusion rate until a predicted plasma concentration of 300 ng/ml was reached. At \( t = 132 \text{ min} \) the transducer did not receive the signal from the arterial line. The three-way valve depicted in Fig. 3.10 was in fact accidentally turned while repositioning the patient. This resulted in MAP artifacts, which were correctly detected. Consequently, the controller did not react by increasing the infusion rate. When artifact-free MAP measurements were again available at \( t = 134 \text{ min} \), they were close to the reference value. At the same time, predicted concentrations were higher
than their reference value. Therefore the controller reduced the infusion rate to 0 ml/h.

Figure 3.15: Closed-loop control performance after intubation. In the upper and middle plots, predicted plasma concentrations $y_1$ and MAP values $y_2$ are represented together with the output constraints and the reference values, respectively. In the lower plot, the infusion rate $u$ is depicted.

Figure 3.16 depicts closed-loop performance during the central phase of the surgery. At $t = 170$ min and $t = 187$ min $y_{1, ref}$ was decreased to 80 and 60 ng/ml, respectively. The anesthesiologist wanted to test whether the same adequate control performance could be achieved with a lower infusion rate. The controller was able to perform adequately with respect to MAP regulation with plasma concentration lower than 100 ng/ml from $t = 170$ min to $t = 200$ min. During skin closure, which started at $t = 203$ min, MAP was rising again. The controller’s reaction brought plasma concentration up again, since MAP has a higher output weight in the controller design.

In the second case considered we examine a 49 years old woman who un-
Figure 3.16: Closed-loop control performance during a clinical study. For a detailed description of the contents of each plot, refer to the caption of Fig. 3.15.

The patient underwent hernia removal. As it can be noticed from Fig. 3.17, the patient revealed to be very sensitive both to surgical stimulation and to alfentanil. Intense and short lasting stimulations at $t = 100, 109, 120, 137, 150, 169$ min respectively triggered quick controller reactions which can be compared to manually administered bolus doses. MAP decreased sharply after each raise in the predicted concentrations. The most evident of these MAP drops occurred at $t = 100$ min, when MAP decreased from the maximum to the minimum allowed level during anesthesia. At $t = 162$ min an artifact in the MAP signal resulting from the flushing of the sampling line was correctly identified.

In Fig. 3.18 the perioperative course of a 49 years old man who was scheduled for hernia removal is depicted. Automatic control was active during the whole period considered in the figure. At $t = 190$ min an arteria was accidentally cut by the surgeon, creating a considerable blood loss and a
3.4 Test of the Controller 115

Figure 3.17: Closed-loop control performance during a clinical study. For a detailed description of the contents of each plot, refer to the caption of Fig. 3.15.

slow decrease in MAP. As it can be noticed from the figure, the automatic controller stopped the infusion rate at \( t = 190 \) min as a result of the hypotensive period. Furthermore, artifacts occurring at \( t = 210, 227 \) and 252 min were correctly detected. The blood loss was not harmful for the patient considered his relatively high BMI.

In Fig. 3.19 the initial phase of the closed-loop drug administration is depicted for a 60 years old female patient. The surgery consisted in removing a spinal tumor located in the proximity of the neck. Automatic control was started at approximately \( t = 8 \) min. We initially set \( y_{1,\text{ref}} = 50 \text{ ng/ml} \) because bolus doses of fentanyl were given before the controller was started. The stimulations occurring at \( t = 8.5 \) min and \( t = 17.5 \) min respectively triggered a controller reaction which led to peaks in the predicted concentrations of approximately \( y_1 = 300 \text{ ng/ml} \). Let us now consider the stimulations occurring after \( t = 55 \) min, where MAP reached the same levels as in...
250
200-
150-
100-
S
100 200 220 240 260

Figure 3.18: Closed-loop control performance during a clinical study. For a detailed description of the contents of each plot, refer to the caption of Fig. 3.15.

the period between $t = 8$ min and $t = 20$ min. Since $y_{1,ref}$ was increased to 100 ng/ml, the controller reacts to surgical stimulation by targeting higher predicted concentrations, as we expected from Fig. 3.9.

In Fig. 3.20 the performance of the closed-loop controller is depicted for the same patient considered before during occurrence of drift artifacts. These artifacts cannot be detected by the PP-approach but they can with the observer-based approach. Drifts in the MAP signal are caused by a vertical, accidental displacement of the three-way valve depicted in Fig. 3.10, with which the MAP signal is calibrated. MAP drifts were artificially generated by the anesthesiologists at $t = 159.5$ min and $t = 161.5$ min, respectively. In the first case, the sensor was moved downwards, leading to low MAP values. In the second case, the sensor was moved upwards, leading to high MAP values. As depicted in the middle plot of Fig. 3.20, the PP values remain in the boundaries for the artifact detection in both situations, be-
Figure 3.19: Closed-loop control performance during a clinical study. For a detailed description of the contents of each plot, refer to the caption of Fig. 3.15.

cause there is no perturbation in the waveform of the blood pressure signal. However, the artifact-based approach was able to detect the sudden change in MAP values, as depicted in the upper plot of Fig. 3.20. Consequently, the controller did not react to such artifacts episodes.

Figure 3.21 shows a clinical validation where the controller successfully avoided overdosing. At $t = 140$ min approximately, a strong surgical stimulation occurred. The controller increased the infusion rate until the upper constraint $y_{1,\text{max}}$ was hit. Even though MAP remained at 110 mmHg for roughly 2 min, the controller decreased the infusion rate during that period to maintain predicted concentration at the upper constraint. Between $t = 160$ min and $t = 190$ min MAP remained constantly higher than the reference value. As a result, the controller targeted predicted concentrations in the range between 200 ng/ml and 300 ng/ml. Despite the constant deviation $\Delta y_2 = y_2 - y_{2,\text{ref}}$, the infusion rate was not constantly increasing until
Figure 3.20: Controller’s performance during drift artifacts. In the upper plot the continuous line represents MAP measurements corrupted by artifacts whereas $y^*(k)$ (•••) represents the values which are fed back to the MPC controller. In the second plot PPs (•••) are plotted together with the upper and lower acceptable value. In the last plot, the infusion rate is depicted.

the upper constraint $y_{1,\text{max}}$ was hit, thus realizing the trade-off depicted in Fig. 3.9.
Figure 3.21: Closed-loop control performance during a clinical study. For a detailed description of the contents of each plot, refer to the caption of Fig. 3.15.
Chapter 4

Modeling of Anesthetic Drug Interactions
Se Esau vendé la primogenitura per un piatto di lenticchie, bisogna dire che il loro uso, come alimento, è antichissimo, e che egli o n’era ghiotto all’eccesso o soffriva di bulimia.

Artusi, *La scienza in cucina e l’arte di mangiare bene.*

**Foreword**

In the introductory section of chapter 1 we rephrased the practice of clinical anesthesia as a complex Multiple Input Multiple Output (MIMO) problem. In chapters 2 and 3 we extracted two essentially decoupled Single Input Single Output (SISO) systems for the closed-loop administration of hypnotics and analgesics, respectively.

The main reasons for adopting such simplifying assumptions emerged from the analysis of the data collected from the clinical study conducted on volunteers. The study protocol was described in detail in chapter 2. The analysis of two particular subsets of the data was performed in chapters 2 and 3. Loosely speaking, there was no evidence in the data that the analgesic alfentanil does systematically affect Bispectral Index (BIS). Similarly, there was no evidence that the volatile hypnotic isoflurane does blunt Mean Arterial Pressure (MAP) reactions to surgical stimulation.

However, nothing excludes that interactions between analgesics and hypnotics may occur. In chapter 2 we documented the case of a patient whose BIS was decreased as a result of a bolus dose of alfentanil. Such an episode leads to an intriguing question: how can we benefit from suspected interaction among anesthetic drugs in an automatic control setting? Two situations may be distinguished. In the first case, like it seems to be happening for anesthesia maintained with isoflurane and alfentanil, interactions are weak and not systematic. In this case sporadic episodes of drug synergies may be compensated without difficulty by letting the two SISO controllers proposed in chapters 2 and 3 run in parallel. In the case where synergies are present, they would be best exploited by automatic control strategies if a model to quantify them would exist. As a matter of fact, the possibility of identifying
an interaction model may be the discriminating criterion between the two cases envisioned above.

The need for a modeling framework to quantify anesthetic drug interactions was the triggering factor of the analysis presented in the following chapter. We will show that existing approaches such as isobolographic methods or multiple logistic regression suffer from significant limitations. On the other hand, the model we propose hinges upon the response surface methodology, which emerges as a better solution for the special case of anesthetic drugs. The interaction model we propose offers several advantages:

- it is suitable to describe different types of interactions such as those between agonists, partial agonists, competitive antagonists and inverse agonists;
- its complexity, as measured by the number of parameters which must be identified, can be tailored to the size of the data set. Precisely, for data sets of limited size the interaction can be described by one single parameter;
- it provides accurate description of the interactions over the whole concentration-response range;
- it is compatible with single drug models when interactions between pairs of anesthetic drugs are considered. In the case of interactions among three drugs, it is also compatible with interaction models between pairs of drugs. Particularly, pharmacodynamic (PD) parameters of both single drug and combination of two drugs can be directly embedded in the three drug interaction model without the need of re-estimating them;

This work was performed in collaboration with several institutions: the Department of Anesthesia and Pain Management at the Royal North Shore Hospital in Sydney, Australia, the Stanford University School of Medicine, California, the Department of Anesthesiology at the University Hospital in Bern, Switzerland and Pharsight Corporation, Mountain View, California. Our contribution at the Automatic Control Laboratory of the Swiss Federal Institute of Technology was to develop the modeling framework for the three drug interaction case. We are precisely indebted to the above mentioned institutions for having involved us in such a challenging project.
The chapter covers the mathematical part of the model for the drug interactions with great detail. A clinical study was conducted to assess synergies among propofol, midazolam and alfentanil. The result of the clinical study and a shorter mathematical description than the one presented in the following chapter appeared as:


A computational and a visualization tool which support the identification of the models presented here can be downloaded from the web site: http://www.anesthesiology.org
4.1 Introduction

Combinations of anesthetic drugs instead of a single agent are widely used in the clinical practice, both during the induction and the maintenance of anesthesia. Before the patient is intubated for instance, already three different drugs may have been already administered: a sedative during premedication, a hypnotic to induce unconsciousness and an analgesic to blunt the hemodynamic reaction to intubation. Maintenance of anesthesia may include continuous administration of a hypnotic and an analgesic, according to the principles that we embedded into the automatic control systems described in chapters 2 and 3.

Several clinical benefits were reported when performing multi-drug anesthesia (Vuyk, 1997). Most of these advantages may result from drug synergies. Loosely speaking, synergy occurs when a combination of two or more agents is capable of achieving the same clinical end-point with less drug amounts than the if single drugs were used alone. In the opposite case, when a combination is less effective than the single agents, we speak about antagonistic interaction. Synergy represents a favorable situation clinically, since most side effects are generally a consequence of drug overdosing.

Beyond the clinical practice, understanding drug synergies may provide significant insight into the mechanisms of general anesthesia (Meyer, 1899; Overton, 1901). In fact, in the light of recently discovered experimental evidences, the concept of anesthesia as a unitary mechanism has been abandoned (Kissin, 1993). Anesthesia must rather be regarded as a series of different, concomitant pharmacological actions. It may be conjectured for instance that drug mixtures exhibiting synergies or antagonism are a clear evidence that drug effect is mainly modulated by ligand-receptor interactions.

Modeling of drug synergies was already considered as a research topic in several biomedical disciplines such as toxicology, environmental pollutants and cancer therapy (Greco et al., 1995). The quantitative approaches which were adopted in these cases can be cast in three different categories (Berenbaum, 1985; Berenbaum, 1989): logistic regression approaches, isobolographic methods and response surface techniques.

The first two approaches reveal unquestionable flaws when applied to anes-
thetic drugs: logistic regression is not mathematically consistent with the single drug case, whereas isobolographic methods often provide descriptions which are limited to a narrow range of concentrations.

In this chapter we propose a new framework to describe anesthetic drug interactions based on response surface methods. First, we review the approaches adopted in the literature, with particular emphasis on logistic regression and isobolographic methods. Precisely, the mathematical deficiencies of such approaches are highlighted. Then we will introduce our modeling approach to quantify two or three drug interactions.

4.2 Isobolographic methods

In the case of two drug interactions, isobolographic methods represent the locus of pairs of two drug concentrations \( (C_A, C_B) \) achieving a determined clinical end-point \( E \). In the case of additive interaction, the isobole is described by the following expression (Loewe and Muischnek, 1926):

\[
\frac{C_A}{EC_{A,E}} + \frac{C_B}{EC_{B,E}} = 1 \tag{4.1}
\]

where \( C_A \) and \( C_B \) represent the drug concentrations of species \( A \) and \( B \) at the effect site, respectively. \( EC_{A,E} \) and \( EC_{B,E} \) are the the effect site concentrations of species \( A \) and \( B \) which are necessary to achieve the end-point \( E \) if used as single agents. The following remarks can be made.

1. Eq. (4.1) is satisfied by choosing \( C_A = \alpha EC_{A,E} \) and \( C_B = (1 - \alpha) EC_{B,E} \), \( \forall \alpha \leq 1 \). That is, in the case of additive interaction, a given end-point \( E \) can be reached by choosing \( (C_A, C_B) \) as complementary fractions of their respective potencies \( (EC_{A,E}, EC_{B,E}) \).

2. If \( C_B = 0 (C_A = 0) \) Eq. (4.1) reduces to \( EC_{A,E} = C_A \) \( (EC_{B,E} = C_B) \), which is nothing but the definition of \( EC_{A,E} \) \( (EC_{B,E}) \). In other words, Eq. (4.1) is compatible with single drug models.

3. If a Hill (Hill, 1910) model is chosen to describe the single drug effect
4.2 Isobolographic methods

relationship

\[ E = E_{MAX} \frac{C_i^{n_i}}{C_i^{n_i} + EC_{50,i}^{n_i}} \quad i = A, B \quad (4.2) \]

then Eq. (4.1) can be rearranged as:

\[ \frac{C_A}{EC_{50,A} \left( \frac{r_{1-r}}{1-r} \right)^{\gamma A}} + \frac{C_B}{EC_{50,B} \left( \frac{r_{1-r}}{1-r} \right)^{\gamma B}} = 1 \quad (4.3) \]

where we set \( r = E/E_{MAX} \). Note that the clinical end-point in Eq. (4.2) may be alternatively expressed as a deviation from the baseline value \( \Delta E = E - E_0 \) instead of \( E \). Consequently, also \( \Delta E_{MAX} = E_{MAX} - E_0 \) would have to be used instead of \( E_{MAX} \). In the following we will keep the simpler notation expressed in Eq. (4.2), since the results which will be derived hold for both notations. Figure 4.1 provides a three dimensional representation of the additive interaction expressed by Eq. (4.3) for a specific set of parameters. Figure 4.2 depicts the corresponding isoboles in the plane of the drug units \( U_i = C_i/EC_{50,i} \quad i = A, B \).

In the case of synergistic interaction, we expect that the drug concentrations in Eq. (4.1) achieving a determined effect \( E \) are such that \( C_i < EC_{i,E} \). The following model was suggested to balance aneux the left side of Eq. (4.1):

\[ \frac{C_A}{EC_{A,E}} + \frac{C_B}{EC_{B,E}} + \alpha \frac{C_A}{EC_{A,E}} \cdot \frac{C_B}{EC_{B,E}} = 1 \quad (4.4) \]

where \( \alpha > 0 \) is a synergy parameter which can be identified from the data. The model is capable of describing antagonistic type of interaction if \( \alpha < 0 \). Figure 4.3 represents 50% isoboles (\( r = 1/2 \)) for several values of \( \alpha \). The higher the synergy parameter \( \alpha \), the more significant the bowing towards the origin. The ratio \( S = \alpha m / o n \), where \( o m \) and \( o n \) are the segments depicted in Fig. 4.3 for the 50% isobole, is often used as a geometric indicator of drug synergy (Greco et al., 1995). If Eq. (4.4) holds, it can be shown that:

\[ S = \frac{\alpha}{2(\sqrt{1+\alpha} - 1)} \quad (4.5) \]

There is a special reason why the 50% isobole is considered to define the geometric indicator in Eq. (4.5). In fact, just in this particular case, the most synergistic drug combination occurs when \( U_A = U_B \).
Eqs (4.1) and (4.4) hinge upon two assumption which severely limit their application to anesthetic drugs. First, it is assumed that both drugs can cause an effect \( E \) if used alone, which if not necessarily true, especially if drugs \( A \) and \( B \) are administered to achieve different clinical end-points. This may be the case for instance if \( A \) is a hypnotic, \( B \) an analgesic and \( E \) is a clinical end-point for hypnosis such as BIS. In this case, we may have \( EC_{B,E} \to \infty \) and Eq. (4.4) trivially reduces to \( EC_{A,E} = C_A \). Further, provided the first assumption is satisfied, both drugs must achieve the same end-effect, as represented for instance by the \( E_{MAX} \) parameter in Eq. (4.2).

Further, Eq. (4.4) is also not capable of describing interactions which result in greater maximum effect or asymmetric behaviour.
4.3 Logistic regression

Logistic models are often used to describe clinical end-point which are discrete by nature, such as probability of movement response, pain and sedation scores. For instance, if the considered clinical end-point is a probability measure, denoted as $P$, then we have:

$$P = \frac{f(C)}{1 + f(C)} \quad (4.6)$$

$P$ is the probability of a certain event, $f(C)$ is a generic function of the drug concentration $C$ such that $f(C) > 0$. If we assume

$$f(C) = e^{\alpha_0 + \alpha \log(C)} = e^{\alpha_0} C^{\alpha} \quad (4.7)$$

Figure 4.2: Isoboles curves corresponding to surface depicted in Fig. 4.1.
where \( \alpha > 0 \), then Eqs (4.7) and (4.6) can be considered equivalent to the Hill model in Eq. (4.2):

\[
E = E_{MAX} \frac{\left( \frac{C_A}{EC_{50,A}} \right)^\gamma}{1 + \left( \frac{C_A}{EC_{50,A}} \right)^\gamma}. \tag{4.8}
\]

The equivalence holds provided that: \( \alpha = \gamma \) and \( \alpha_0 = -\gamma \log(EC_{50}) \). With Eq. (4.7) \( C = 0 \) implies \( P = 0 \).

The extension of Eq. (4.7) to describe additive interactions between two drugs can be formulated as follows:

\[
\text{logit } P = \log \left( \frac{P}{1 - P} \right) = \alpha_0 + \alpha_A C_A + \alpha_B C_B. \tag{4.9}
\]

One positive aspect of Eq. (4.9) is that the 50 \% isobole (\( P = 0.5 \)) is the
4.4 The two drugs interaction model

straight line

\[ C_B = -\frac{\alpha_0}{\alpha_B} - \frac{\alpha_A}{\alpha_B} C_A \]  

(4.10)

as we expect for symmetry with additive models described in the previous section. One major flaw of Eq. (4.9) is that, in the absence of both drugs, the clinical end-point has the non-zero probability \( P = e^{\alpha_0}/(1 + e^{\alpha_0}) \).

A straightforward correction to such deficiency would be to use the following additive model:

\[ \text{logit } P = \alpha_0 + \alpha_A \log(C_A) + \alpha_B \log(C_B) \]  

(4.11)

instead of Eq. (4.9). In this case however, the 50 \% isobole is bowed towards the origin, independently from the choice of the parameters. Precisely, we have:

\[ C_B = \frac{e^{\frac{-\alpha_0}{\alpha_B}}}{C_A^\alpha_B}. \]  

(4.12)

Eq. (4.12) also implies that either drug must have an infinite concentration to reach 50 \% of the maximum effect if used alone.

The following modification of Eq. (4.11) was proposed by McEwan and Lang:

\[ \text{logit } P = \alpha_0 + \alpha_A \log(1 + C_A) + \alpha_B \log(1 + C_B). \]  

(4.13)

The additive constant added inside the logarithm of each drug concentration was presumably introduced to have \( \log(1 + C_A) = 0 \) if \( C_A = 0 \). However, the bowing towards the origin remains, since Eq. (4.13) can be merely regarded as a shift of Eq. (4.11) in the plane of the drug concentrations \( (C_A, C_B) \).

4.4 The two drugs interaction model

Before introducing the new model, let introduce the definition of units of drugs A and B:

\[ U_A = \frac{C_A}{EC_{50,A}} \quad U_B = \frac{C_B}{EC_{50,B}} \]  

(4.14)
Then, let us define a fixed combination of drugs $A$ and $B$ with the fractional unit:

$$\theta = \frac{U_B}{U_A + U_B}. \quad (4.15)$$

The model we propose hinges upon two main assumptions. First, a fixed combination of drugs ($\theta = \text{const.}$) can be regarded as a new drug. Second, this new drug follows a Hill model when the total concentration is increased while maintaining a fixed drug fraction $\theta$. Extending the Hill model in Eq. (4.2) to describe this two drug interaction we have:

$$E = E_{MAX}(\theta) \frac{\left( \frac{U_A+U_B}{U_{50}(\theta)} \right)^{\gamma(\theta)}}{1 + \left( \frac{U_A+U_B}{U_{50}(\theta)} \right)^{\gamma(\theta)}} \quad (4.16)$$

where $\gamma(\theta)$ and $E_{MAX}(\theta)$ are the steepness and the maximum effect parameters of the drug combinations. $U_{50}(\theta)$ is the potency of the drug combination relative to the normalized potency of each drug by itself. In order to clarify this, let us first observe the limit case when $\theta = 1$. In this case, Eq. (4.16) must reduce to the Hill model for the single drug in Eq. (4.2). To achieve this, we must have $U_{50}(1) = 1$. Similar arguments when $\theta = 0$ would lead to $U_{50}(0) = 1$. Let us assume that there is no synergy at the maximum effect $E_{MAX}$. Further, let us consider the case when both drugs are present each at exactly half of their respective potencies. That is, $U_A = 1/2$ and $U_B = 1/2$. The total number of drug units in this case is $U_A + U_B = 1$. If $U_{50}(1/2) = 1$ the total effect is such that $E = E_{MAX}/2$. That is, the total effect depends on the total number of units rather than the number of units of each drug separately. If $U_{50}(\theta) = 1$ for a given $\theta$, we speak about additive interaction of the drug potencies at that ratio. If $U_{50}(\theta) \equiv 1 \quad \forall \theta \in [0, 1]$, the combination exhibits additive interaction. If $U_{50}(\theta) < 1$, the number of ‘effective’ drug units $(U_A + U_B)/U_{50}$ is greater than the total number of units $U_A + U_B$. In this case we speak about synergistic interaction. Conversely, if $U_{50}(\theta) > 1$, we speak about antagonistic interaction.

The simplest expression for $U_{50}(\theta)$ which accommodates for the boundary conditions $U_{50}(0) = U_{50}(1) = 1$ and is able to exhibit non additive interaction is:

$$U_{50}(\theta) = 1 - \beta \theta + \beta \theta^2. \quad (4.17)$$
Synergy in Eq. (4.17) occurs if $\beta > 0$. Let us assume that this is the case in the following discussion. Two properties of Eq. (4.17) are worth to be mentioned.

1. $U_{50}(\theta) = U_{50}(1-\theta)$. That is, the maximum synergy occurs necessarily at $\theta = 1/2$ and there is a symmetric behaviour with respect to the drug combination of equal units. In other words, combinations such that $U_A = a$ and $U_B = b$ or $U_A = b$ and $U_B = a$ are equivalent.

2. Let us assume that there is no interaction at the $E_{MAX}$ parameter and that $E_{MAX,A} = E_{MAX,B} = E_{MAX}$. That is, $E_{MAX}(\theta) \equiv E_{MAX} \forall \theta$. In this case, the point of maximum curvature of the 50% isobole in the plane $(U_A, U_B)$ occurs for $U_A = U_B$. Figs 4.4 and 4.5 represent the surface response and the isoboles for a particular choice of the set of parameters. For the 50% isobole we have:

$$S = \frac{4}{(4 - \beta)}.$$ (4.18)

From Eq. (4.18) we also derive $\beta < 4$.

3. The synergy parameter $\beta$ in Eq. (4.17) can be estimated directly from the 50% isobole. In fact, on this curve, according to Eq. (4.16) it must be $U_A + U_B = U_{50}(\theta)$. Precisely:

$$U_A^3 + U_B^3 + U_A^3(3U_B - 1) + U_B^3(3U_A - 1) = (\beta + 2)U_AU_B.$$ (4.19)

$\beta$ be estimated with standard linear regression algorithm from the previous expression.

If Eq. (4.17) is too restrictive, in the light of the discussion above, higher order polynomial can be used. However, if $U_{50}(\theta) \in \mathbb{P}^n$, $n - 1$ parameters must be identified. This may be difficult, considered the extreme interindividual variability and the cost of every data point. In Eq. (4.17), testing synergy is limited to the test of a single parameter.

Analogous arguments hold for the definition of $\gamma(\theta)$ and $E_{MAX}(\theta)$. Similarly to Eq. (4.17), we may define

$$\gamma(\theta) = \gamma_A + (\gamma_B - \gamma_A - \beta)\theta + \beta\theta^2,$$ (4.20)

$$E_{MAX}(\theta) = E_{MAX,A} + (E_{MAX,B} - E_{MAX,A} - \beta)\theta + \beta\theta^2.$$ (4.21)
4.4 The three drugs interaction model

For the three drugs interaction model, the same concepts and assumptions described in the previous section apply. For any fixed ratio of the drugs $A, B, C$ a simple Hill model describes the concentration vs. effect relationship. That is:

$$E = E_{MAX}(\theta) \frac{\left( \frac{U_A + U_B + U_C}{U_{50}(\theta)} \right)^{\gamma(\theta)}}{1 + \left( \frac{U_A + U_B + U_C}{U_{50}(\theta)} \right)^{\gamma(\theta)}}$$

(4.22)

In this case, however, a combination is uniquely defined when the drug fractions of two among the three drugs in the mixture are specified. We
4.5 The three drugs interaction model

Figure 4.5: Isoboles curves corresponding to surface depicted in Fig. 4.4.

may choose:

$$\theta_B = \frac{U_B}{U_A + U_B + U_C}, \quad \theta_C = \frac{U_C}{U_A + U_B + U_C}. \quad (4.23)$$

Obviously $\theta_A = 1 - \theta_B - \theta_C$. For a fixed drug combination, we seek appropriate functions $E_{MAX}(\theta_B, \theta_C)$, $\gamma(\theta_B, \theta_C)$ and $U_{50}(\theta_B, \theta_C)$ which meet the following specifications.

1. If $\theta_A = 0$, the three drugs interaction model should resolve mathematically to the interaction model between drugs $B$ and $C$. Analogous arguments must hold if $\theta_B = 0$ or $\theta_C = 0$.

2. If there is an additive interaction among the three drugs, then $U_{50} \equiv 1$.

3. Consider a sham experiment in which drugs $B$ and $C$ are actually the same drug, a drug that shows synergy with drug $A$. In this sham experiment, the interaction of $A$ with any combination of $B$ and $C$ should yield the same interaction as the interaction between $A$ and $B$ or $A$ and $C$. 


4. The model should be symmetrical with regards to A, B and C. In other words, it should meet the above specified criteria regardless of which drug is assigned as A, B and C.

We propose a model where interaction parameters $E_{MAX}(\theta_B, \theta_C)$ and $U_{50}(\theta_B, \theta_C)$ are described at most by a parabola. Even though higher order polynomials would give more flexibility, it may be hard to identify all the parameters from experimental data with sufficient accuracy. Every interaction parameter can be described by the following polynomial:

$$P = q_0 + q_B \theta_B + q_C \theta_C + q_{BB} \theta_B^2 + q_{CC} \theta_C^2 + q_{BC} \theta_B \theta_C + q_{ABC} \theta_A \theta_B \theta_C$$

(4.24)

Few properties of Eq. (4.24) can be highlighted.

1. The model is polynomial, therefore smooth and infinitely differentiable.

2. The model is a function of $\theta_B$ and $\theta_C$, because $\theta_A = 1 - \theta_B - \theta_C$. $\theta_A$ is expressed in the last term for clarity. The term $q_{ABC}$ can be regarded as the ‘three drug interaction term’, since it vanishes on each axis of the triangle of compositions, that is when pairs of drugs are considered.

3. The last term $q_{ABC} \theta_A \theta_B \theta_C$ in Eq. (4.24) can be substituted with the more general expression $\theta_A \theta_B \theta_C f(\theta)$, where $f(\theta)$ is a general function of the composition vector $\theta$. This term satisfies the same property of vanishing on the axes and enables more flexibility with the choice of $f(\theta)$.

Since for the three drugs interaction case of Eq. (4.22) the effect is a function of three independent variables, the effect surface response cannot be represented graphically. However, since the interaction parameters were assumed to depend on the composition of the mixture, a three dimensional representation is possible. Figure 4.6 depicts the composition triangle which is used for three dimensional representations. Every point inside the triangle defines a drug composition such that $\theta_A + \theta_B + \theta_C = 1$. Figure 4.7 represents the interaction parameter $P = E_{MAX}$ for a particular drug combination exhibiting antagonism. Figure 4.8 represents the interaction parameter $P = U_{50}$ for a particular drug combination exhibiting synergy.
4.5 The three drugs interaction model

Figure 4.6: Three drugs composition triangle to represent the interaction parameters \( E_{MAX}(\theta_B, \theta_C), \gamma(\theta_B, \theta_C) \) and \( U_{50}(\theta_B, \theta_C) \). Every side of the triangle is assumed to have unitary length. The fraction of each drug can be obtained by projecting the point \( p \) along the three axis. It can be easily verified that \( \theta_A + \theta_B + \theta_C = 1 \).

Eq. (4.24) was developed by assuming that for every pair of drugs the interaction model is known and has the form:

\[
P_{AB} = P_A + (P_B - P_A - \beta_{AB})\theta_B + \beta_{AB}\theta_B^2 \\
P_{AC} = P_A + (P_C - P_A - \beta_{AC})\theta_C + \beta_{AC}\theta_C^2 \\
P_{BC} = P_B + (P_C - P_B - \beta_{BC})\theta_C + \beta_{BC}\theta_C^2
\] (4.25, 4.26, 4.27)

where \( P_A, P_B \) and \( P_C \) are the parameters of the single drugs when given alone, and \( \beta_{AB}, \beta_{AC} \) and \( \beta_{BC} \) are the coefficients for the three paired interactions. By imposing the surface in Eq. (4.24) to become Eqs (4.25, 4.26, 4.27) when \( \theta_C = 0, \theta_B = 0 \) and \( \theta_A = 0 \) respectively, we obtain the following set
Figure 4.7: Interaction parameter $E_{MAX}(\theta_B, \theta_C)$ for a drug combination such that: $E_{MAX,A} = 3$, $E_{MAX,B} = 3.5$, $E_{MAX,C} = 4$, $\beta_{AB} = 3$, $\beta_{AC} = 3.5$, $\beta_{BC} = 2$, $\beta_{ABC} = 5$.

of constraints:

\begin{align*}
P_A &= q_A 
\quad (4.28) \\
P_B &= q_A + q_B + q_{BB} 
\quad (4.29) \\
P_C &= q_A + q_C + q_{CC} 
\quad (4.30) \\
\beta_{AB} &= q_{BB} 
\quad (4.31) \\
\beta_{AC} &= q_{CC} 
\quad (4.32) \\
\beta_{BC} &= q_{CC} + q_{BB} - q_{BC} 
\quad (4.33)
\end{align*}

Eqs (4.28,4.33) represent a linear system of order 6. This was expected, since the parameters we imposed equivalence with are single drug parameters ($P_A, P_B, P_C$) and the paired interaction parameters ($\beta_{AB}, \beta_{BC}, \beta_{AC}$). Since the interaction models for the three different pairs of drugs are known by
4.5 The three drugs interaction model

Figure 4.8: Interaction parameter $U_{50}(\theta_B, \theta_C)$ for a drug combination such that: $\beta_{AB} = 0$, $\beta_{AC} = 2$, $\beta_{BC} = 1$, $\beta_{ABC} = -2$.

assumption, Eqs (4.28,4.33) can be inverted to give:

\[
\begin{align*}
q_0 &= P_A \\
q_B &= P_B - P_A - \beta_{AB} \\
q_C &= P_C - P_A - \beta_{AC} \\
q_{BB} &= \beta_{AB} \\
q_{CC} &= \beta_{AC} \\
q_{BC} &= \beta_{AB} + \beta_{AC} - \beta_{BC}.
\end{align*}
\]

There is just one left parameter to be specified in Eq. (4.24), the three term interaction $q_{ABC}$. Testing of synergy resolves to testing significance of one single parameter, in analogy with the two drugs interaction case. If experimental data justify the use of more involved types of expressions in Eq. (4.24), then the term $f(\theta)$ may be used instead. It can be verified that Eq. (4.24) satisfies both the symmetry condition and the condition.
expressed by the sham experiment. Since verification of such statements is just a matter of simple algebraic manipulations, the details are omitted for brevity.
Chapter 5

Conclusions
Slugs and snails are after me, DDT keeps me happy
Now I guess I'll have to tell 'em that I got no cerebellum.
Gonna get my Ph.D. I'm a teenage lobotomy.


### 5.1 Main achievements

This thesis described the recent developments of automatic control application in the realm of anesthesia. Two model-based feedback controllers were thoroughly discussed for the closed-loop administration of hypnotics and analgesic drugs. To the best of the author's knowledge, both are the first model-based controllers ever applied on humans for the purposes described in the thesis. We discussed the above mentioned controllers not only presenting their technical aspects, but we also demonstrated their clinical feasibility on patients undergoing general surgery.

This thesis also discussed an important contribution to the study of anesthetic drug interactions. We introduced an adequate modeling framework to quantify pharmacodynamic (PD) interactions among two and three drugs combinations.

In this final chapter we summarize the main results achieved. A separate section is associated to every chapter of the thesis. The section title is the same as the chapter title. In every section we discuss the limitations of the approaches proposed in the corresponding chapters while suggesting some directions for future research. We also focus on the impacts that the approaches presented may have on other research applications and on the clinical practice.
5.2 Automatic control in anesthesia

5.2.1 Main achievements

In chapter 1 the steps towards the development of an autonomous anesthesia system taken at our laboratory were described. As a result of a solid cooperation with the University Hospital in Bern, we can evaluate the clinical benefits of closed-loop controllers which regulate seven different patient's outputs. To date, more than 200 patients were treated with closed-loop controllers during general anesthesia. These controllers regulate $O_2$, $CO_2$, inspired and expired anesthetic gas concentrations in the breathing system, Bispectral Index (BIS) and Mean Arterial Pressure (MAP) with both volatile and intravenous anesthetic agents.

Two controllers which use isoflurane as anesthetic drug were described in this chapter. Both aim at regulating the depth of hypnosis using MAP and BIS as surrogate measures. The controllers adopt particular schemes to prevent overdosing in the clinical practice and guarantee safe operation in the presence of measurement artifacts. The controllers also adapt to the different operating regimes of the breathing system, guaranteeing adequate performance. The successful application of both controllers in the clinical practice was shown, indicating a higher quality anesthesia for subjects who were treated with automatic control.

5.2.2 Outlook

Chapter 1 raises the question whether there will be a time when closed-loop drug administration will be routinely adopted in the operating room. Assuming technical perfection and guaranteed safety of the proposed administration schemes, two obstacles must be overtaken.

On one hand, anesthesiologists must be persuaded that automation in this field is not aimed at removing professional figures. Rather, by relieving the personnel from routine tasks, it helps physicians to be more focused on critical situation. As an anesthesiologist in Bern often claims: "...anesthesia is 99% boring and 1% panic". Needless to say that automatic controllers
cannot take over during emergency situations. However, they can improve the working quality for the 99% of the time.

On the other hand, patients must be convinced that undergoing surgery with automatic controllers represents a clear advantage both for her/his perioperative and postoperative period. We found that convincing a patient about the advantages of closed-loop drug delivery is quite straightforward, provided the anesthesiologist is convinced first. We feel that most of the persuasive power lies in the enthusiasm and in the confidence of physicians. To obtain informed consent from patients for the clinical evaluation of our controllers, it often sufficed to face them with the following dilemma: “Given that you would never travel across the ocean without a pilot in the cockpit, would you prefer to fly with or without an automatic controller aboard?”. Having grasped the analogy between the flight and the dive into unconsciousness, most patients accepted favorably the automatic controller.

5.3 Feedback control of hypnosis

5.3.1 Main achievements

In chapter 2 the cascaded closed-loop controller to regulate hypnosis assessed with BIS with isoflurane was thoroughly discussed. Volatile agents such as isoflurane have slower onset and require more cumbersome actuators than intravenous drugs such as propofol. However, concentrations in the central compartment can be measured on-line. This advantage was exploited by the proposed cascaded Internal Model Control (IMC) structure: the control system has an internal closed-loop controller for endtidal concentrations which dominates if BIS measurements are corrupted by artifacts.

We showed that for our particular application, both the cascade arrangement and the model-based approach to control offer several advantages over other techniques. First, it permits useful off-line model validation and analysis. Second, it allows to adapt the controller to the different respiratory conditions in a straightforward manner. Third, it also provided an easy framework to design artifact-tolerant controllers. Fourth, the controller is capable of limiting endtidal concentrations between a lower and an upper
5.3 Feedback control of hypnosis

limit to prevent the patient from awareness and to avoid overdosing, respectively. Fifth, anti-windup measures protect the control scheme against performance degradation in the event of saturation of the input signal. Summarizing, we were able to show satisfactory performance of the BIS controller during general anesthesia. We believe that the clinical validation of the controller will also confirm the usefulness of BIS monitors as a guide for the closed-loop administration of hypnotic agents.

5.3.2 Outlook

Not withstanding their increasing popularity in the clinical practice, BIS monitors may not be the ultimate chapter in the seek of monitors for the depth of hypnosis. Other indicators such as Auditory Evoked Potentials (AEP) may reveal advantages with respect to BIS monitors in particular situations. As recent studies seem to suggest, they may be more reliable in the region of light sedation and react more promptly in detecting an arousal reaction (Gajraj et al., 1999). A natural research direction to pursue in this case would be to design closed-loop controllers which deliver hypnotics on a basis of a degree of hypnosis estimated from multiple sensors. If designed properly, those controllers may not only provide a better patient care, but they may give important insight into the nature of drug induced unconsciousness.

It can be argued that on-line identification of the patient’s specific characteristics may improve the controller’s performance. For instance, identifying whether a subject is particularly sensitive to the drug may suggest the need for detuning the controller to prevent overdosing. These ideas are currently being explored in our research project and will be published in future works.

The proposed control structure is not limited to isoflurane. In fact the same approach could be adopted for any volatile anesthetic as long as the appropriate pharmacokinetic-pharmacodynamic (PK-PD) model is used. This makes it an ideal design for other clinical situations such as pediatric anesthesia where other volatile agents are used.

A feasible extension of the proposed approach would consist in including other physiological variables such as MAP in the decision algorithm for drug administration. In general, we can not allow excessively low MAP
while the drug is administered to maintain a desired level of BIS. A simultaneous closed-loop control of BIS and MAP may be designed to address the above mentioned issues. An override arrangement, equivalently to the one presented for control of MAP and endtidal concentrations in chapter 2 may serve the desired purposes. Alternatively, vasoactive drugs may be infused to compensate for the hypotensive or hypertensive periods.

5.4 Feedback control of analgesia

5.4.1 Main achievements

In chapter 3 we introduced a new paradigm for the closed-loop administration of opiates during surgery. The control system aims at regulating both MAP and predicted plasma concentration, realizing an adjustable trade-off between open- and closed-loop administration schemes. An MPC control algorithm was adopted, which is capable of handling complex control objectives such as input/output constraints and drug minimization. Anesthesiologists are able to adjust output constraints to the intensity of surgical stimulation or to the patient’s characteristics.

The explicit formulation of the MPC problem was considered for the implementation of the control algorithm in the real-time platform, which gives more insight about controller behaviour for a particular choice of the observer’s states, output and references values, respectively. Also, it allows to show the relationship between the optimization weights in the MPC algorithm and the control action in a more transparent way. Among the advantages of the proposed control strategy, we want to stress that this approach may be adopted for any other analgesic drugs by simply using a different PK-PD model in the MPC algorithm.

An observer- and a signal-based artifact detection algorithm were implemented in the closed-loop system. The controller is therefore capable of handling MAP artifacts during surgery and consequently to protect the patient from hazardous controller’s behaviour. The results of the application of the controller on humans were presented which show an excellent performance of the administration scheme.
5.4 Feedback control of analgesia

5.4.2 Outlook

As pointed out in the chapter, and much more in this case than for hypnotics, the optimal indicator of the analgesic drug effect is the major lack to be compensated. Even though analgesic drugs are primarily administered to obtund hemodynamic reaction to surgical stimulations, MAP may not be the optimal clinical end-point for opiate infusion. In this respect, an approach using several hemodynamic variables such as HR, cardiac output and blood pressure signal simultaneously may reveal advantages with respect to the scheme presented here.

There have been numerous attempts to rate the analgesic state of the patient from hemodynamic variables. None of them seems to have emerged as a stand-alone indicator for closed-loop delivery, probably because cardiovascular signals like MAP are modulated by numerous other factors beyond insufficient analgesia such as biological feedback regulation and vasoactive drugs.

Alternatively, one may use Somatosensory Evoked Potentials (SEP) for the closed-loop infusion of analgesic drugs, which may also provide insight both into the nature of perception of noxious stimulation during unconsciousness and into the influence of opiates on the autonomic system reaction (Thorpe, 1984). A considerable benefit may result from performing such investigations in a future research. Also, one may ascertain whether the costs of an additional monitoring technique are outweighed by a better infusion regime of intravenous analgesics.

The infusion policy we presented for analgesic drugs could be extended to define new therapies for insulin-dependent diabetes subjects. As we described in the chapter, the control strategy realizes an adjustable trade-off between an open- and a closed-loop infusion policy. The open-loop policy is determined by a drug distribution model which is highly uncertain. The closed-loop policy is determined by a measurement of difficult interpretation such as MAP. The same premises hold for state-of-art insulin therapies. The open-loop infusion regimen is determined by an experienced physician who prescribes insulin injections on the basis of the patient’s lifestyle. The doses of the single injections are adjusted on the basis of sparse blood glucose concentration measurements taken by the patient. This constitutes a closed-loop adjustment to the open-loop policy. The control system for infusion
of analgesics can be rephrased with the terminology of insulin therapy by substituting MAP with blood glucose measurements. Also, predicted concentrations of analgesics must be substituted by concentrations of glucose predicted by a dynamic model of the glucose-insulin system. If used in the insulin therapy context, the Model Predictive Controller (MPC) presented in the chapter would allow to handle constraints both for predicted and measured variables. This makes it ideal for insulin therapy, since hypoglycemic or hyperglycemic episodes may be ruled out in the same way underdosing or overdosing of analgesic drugs were in the closed-loop strategy presented in the chapter.

Another interesting research opportunity unearthed by the closed-loop validation of the controller lies in some aspects of the artifact detection/prediction problem for physiological signals, which were not covered by this and previous works (Frei, 2000). In fact, even though model-based approaches for artifact handling can be easily implemented as extensions of model-based control strategies, they are still inherently coupled with the particular control strategy for which they were designed. Further, for observer-based methods, their correct operation is guaranteed if and only if artifacts lead to transients in the residual dynamics which are faster than those triggered by surgical stimulation or other physiological events. As we showed with a clinical example, this assumption may not always be true. We did introduce a signal-based algorithm, which compensates for such limitation. We believe that an artifact detection approach which is solely based on the beat to beat blood pressure signal sampled at high frequencies (> 50 Hz) may represent a feasible solution for control purposes. Several methods based on frequency and time techniques have already been successfully applied for several purposes. A major advantage of such approach would be that - at least for the detection part - the method would be entirely decoupled from the particular control application considered. This issue may be addressed in the future of the research project.
5.5 Modeling of anesthetic drug interactions

5.5.1 Main achievements

In chapter 4 a new modeling framework to quantify anesthetic drugs interactions was proposed. The approach we described overcomes the limitations of other methods which were applied in other biomedical disciplines such as isobolographic methods or multiple logistic regression techniques. The framework we proposed stems from the response surface methodology, which emerges as a better solution for the special case of anesthetic drugs. It is suitable to describe different types of interactions such as those between agonists, partial agonists, competitive antagonists and inverse agonists. The model complexity, as measured by the number of parameters which must be identified, can be tailored to the size of the data set. Precisely, for data set of limited size interaction can be described by one single parameter. Finally, it is compatible with previously identified model parameters for single and pairs of anesthetic drugs.

5.5.2 Outlook

Even though the presented models have already been used to explore hypnotic synergies among midazolam, propofol and alfentanil, several other investigations need to be carried out before automatic controllers can exploit these synergies. Just when this stage is attained, it will be possible to exploit the benefits of multi-drug anesthesia in automatic control algorithms. As an example, opiates often potentiate the hypotensive effects of isoflurane (Vuyk, 1997). In a control scheme where hypotension is regulated by volatile hypnotic agents, closed-loop administration of small doses of opiates may lead to the same therapeutic effect with less drug consumption.

5.6 The advantages of model-based controllers

All the control schemes presented in this thesis were designed with model-based approaches. It is natural to ask whether such control strategies have
a real advantage over more classical control techniques such as simple PID of fuzzy controllers. The author of this thesis is inclined to believe they do.

A first advantage of model-based control strategy is represented by the ease of tuning. Even though model-based control schemes require a more involved implementation, they are easier to tune than other techniques and easier to adapt to changes in the operating regimes. An example was provided by the cascaded IMC controller described in chapter 2, where anesthesiologists can tune the controller to match their expected performance without the help of the system engineer and where online model adaptation is able to compensate for changes in the actuator dynamics. Second, model-based control techniques provide an elegant and easy framework to design artifact and fault tolerant control schemes. Third, model-based control techniques provide a straightforward framework to implement complex control objectives such as multiple output regulation, drug minimization, handling of input and output constraints. We demonstrated the multitasked features of the MPC controller with the clinical experiments discussed in chapter 3.

The fact that model-based techniques need a dynamic model is a pleonasmus which may be worth to spell out. As we showed in chapter 2, identification of accurate models for the drug distribution and effect is made difficult by the cost of experimental studies, the lack of measurements which reduces the number of parameters which can be identified and the extreme interindividual variability. It is naive to say if not erroneous, though, that alternative non model-based strategies do not require a model. In fact, before testing our controllers on humans, extensive simulation of the closed-loop performance is necessary. For this purpose, a model or a model class for the drug distribution and effect must be postulated also when non model-based techniques are adopted.

Model-based control techniques make use of dynamic models to predict the future behaviour of the patient’s physiological outputs. These models mirror more or less accurately the anesthesiologist’s clinical experience and their use improves the physicians’ confidence in automatic control strategies. However, the control algorithm ‘per se’ is less transparent with such approaches when compared to non model-based techniques. For instance, even for the expert system engineer it is difficult to estimate, on the basis of the actual output measurements what will the IMC controller described in chapter 2 choose as the next input action. On the other hand, the control
actions computed by a fuzzy controller may be easier to predict. Anesthesiologists tend to prefer control schemes where they are able to predict, in parallel with the controller, the future input moves. These strategies may include fuzzy or rule-based controllers. This attitude is understandable if one considers that the control algorithm will substitute the physician in the decision process.

However, this does represent a limitation more than an advantage both from a research and a clinical perspective. There are at least two reasons for that. Let us consider as an example using a fuzzy controller for closed-loop drug delivery during anesthesia. First, tuning a fuzzy controller boils down to reproducing the anesthesiologists’ set of rules to administer drugs. These set of rules are not only hardly countable but also based on intuition, which is not translatable into any fuzzy rule. Moreover, every physician develops her/his set of rules according to the clinical experience, the drugs commonly used in the operating room and the equipment provided by the hospital. In the end, the tuning process can be virtually endless. Second, a fuzzy controller is tuned to match a predetermined infusion policy. On the contrary, model-based controllers are tuned on the basis of the desired closed-loop performance. This makes them capable of revealing new administration strategies which could not be unearthed by a fuzzy controller.

Another limitation shared by both fuzzy and classical PID controllers lies in their non systematic approach to handle input and output constraints. As an example, let us consider the regulation of MAP with isoflurane described in chapter 1. Constraints for endtidal gas concentrations were handled by two additional controllers connected to the main controller in an override scheme. The same problem was solved in the closed-loop control of BIS presented in chapters 1 and 2 by using a saturation element for endtidal concentration references in the cascade scheme. In the MPC controller presented in chapter 3, the multiple constraints for the input and both output signals were handled in a coherent way. Also, it was possible to introduce a prioritization in the output constraints according to the clinical severity of the constraint violation. Every control application must deal with constraints efficiently in order to guarantee reliability. This is particularly true for control schemes applied to biological systems, where higher safety standards are required. For those purposes, as we showed in this thesis, MPC emerges as the natural strategy for control.
Bibliography


Bibliography


Bibliography


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Highlights

Chemical engineering:
- expertise in modeling and design of chemical processes, thermodynamics, industrial chemistry, transport phenomena and numerical methods for partial differential equations.
- research experience in chromatography, particularly in the separation of pharmaceutical enantiomers.

Electrical engineering:
- extensive knowledge of control systems technology.
- expertise in the design of linear, robust, Multivariable, Model Predictive (MPC), Internal Model (IMC), H infinity ($H_\infty$) and frequency domain based controllers.
- demonstrated ability in implementing finite state machines, I/O drivers and fault tolerant control structures for real time applications.
- proven ability in performing experimental studies on humans.
- strong background in signal process analysis, with experience in physiological signals.

Biomedical engineering:
- in depth knowledge of mathematical statistics, with expertise in identification methods, regression analysis and multivariate observations.
- strong background in Pharmacokinetic-Pharmacodynamic modeling, with special emphasis on anesthetic drugs.
- expertise in modeling and operation of drug administration devices.

Education

Department of Electrical Engineering,
Swiss Federal Institute of Technology (ETH), Switzerland.

Thesis: “Feedback Control of Hypnosis and Analgesia in Humans”.

Results:
- realization of a platform for computer-aided anesthesia.
- modeling of the distribution and effect of anesthetic drugs.
- development of a modeling framework for anesthetic drugs interactions.
- design of the first model-based closed-loop controllers for the administration of hypnotics and analgesics.
- extensive controllers’ validation in humans.
Department of Mathematics.
Swiss Federal Institute of Technology (ETH), Switzerland.
Thesis: “Time Frequency Representation of EEG during Painful Electrical Stimulation”.

Sep. 1998 - Sep. 2000: Postgraduate degree in Information Technology
Department of Electrical Engineering.
Swiss Federal Institute of Technology (ETH), Switzerland.
Thesis: “Modeling and Closed-loop Control of Hypnosis by Means of Bispectral Index with Isoflurane”.

Sep. 1991 - Feb. 1997: M.S. degree in Chemical Engineering
Department of Chemical Engineering.
Politecnico di Milano, Italy.
Thesis: “Continuous Chromatography of Binary Mixtures with Variable Selectivity: Design of the Operating Conditions”.
Final mark: 100/100 “summa cum laude”.

Liceo Scientifico Vittorio Veneto in Milano, Italy.
Final mark: 60/60.

Work experience

Apr. 1997 - Dec. 2000: Teaching Assistant
Automatic Control Laboratory, Department of Electrical Engineering.
Swiss Federal Institute of Technology (ETH), Switzerland.
Tasks: - preparation and oral presentation of lectures and exercises on linear Algebra, linear and non-linear control systems.
- organization, preparation and evaluation of written exams.
- supervision of students during laboratory experiments.

Automatic Control Laboratory, Department of Electrical Engineering.
Swiss Federal Institute of Technology (ETH), Switzerland.
Task: Ph.D. candidate under the supervision of Prof Dr. Manfred Morari.


GWM S.p.A., Italy.
Tasks: - development of E.U. quality certification for automatic spindle machines.
- development of technical solutions to improve the operational safety.
- author of both technical and operating manuals.
Grants, Patents and Awards

Title: “Arrangement and process for controlling a numerical value for patient respiration”.
Submitted to the U.S. patent office.

Title: “Layout of an automatic controller for the regulation of a patient’s numerical value with autonomous respiratory systems”.
Submitted to the E.U. patent office.


Sep. 1997: Co-recipient of the Swiss National Science Foundation 32-51028.97 grant.

Award: distinguished undergraduate academic record.

Computer Skills

Operating systems: extensive experience with Unix, Windows and X Oberon.

Programming languages: in depth knowledge of Matlab, S-Plus, Oberon, Fortran, C.

Text formatting: \LaTeX, Microsoft Office and Adobe Acrobat packages.

I/O interfaces: demonstrated ability in implementing data communication through RS-232 and TCP/IP protocols.

Real-time systems: strong experience in the design of closed-loop controllers and finite state machines for real-time applications. Implementation in Oberon.

Networking technology: expertise in FTP, TFTP, telnet.

Web publishing: expertise in Web pages design with HTML.

Languages

English: writing and speaking fluently.

French: writing and speaking fluently.
Jan. 1996: obtained “Certificat d’études de la Langue Française” (CELF) from the “Centre culturel français” in Milano, Italy.

German: writing and speaking fluently.

Italian: mother tongue.
Biographical sketch:

Dec. 1972 : Born in Livorno, Italy.
Apr. 1997 - present : Zürich, Switzerland.

Objective:
Looking for a dynamic environment where fast learning and interaction with people is must.

Skills:
Extensive experience in communicating with medical doctors, researchers and support staff. Able to find out new opportunities in the medical field and provided new engineering solutions which improve both the patient care and anesthesiologists’ working environment. I am known for getting things done.

Recreational activities:
I am a triathlete, a marathon runner, a certificate diver and a skier. Also, I enjoy interacting with people, reading and sports.
List of Publications

Journal Papers

Chemical Engineering Publications

A. Gentilini, C. Migliorini, M. Mazzotti and M. Morbidelli.
“Optimal Operation of Simulated Moving-Bed Units for Non-linear Chromatographic Separations II. Bi-Langmuir Isotherm”.

C. Migliorini, A. Gentilini, M. Mazzotti and M. Morbidelli.
“Design of Simulated Moving Bed Units under Non-ideal Conditions”.

Anesthesia and Electrical Engineering Publications

A. Gentilini, C.W. Frei, A.H. Glattfelder, M. Morari and T.W. Schnider.

“Artifact-Tolerant Controllers for Automatic Drug Delivery in Anesthesia.”

“Response Surface Models for Anesthetic Drug Interactions”.

“Multitasked Closed-Loop Control in Anesthesia”.

A. Gentilini, M. Rossoni-Gerosa, C. Frei, R. Wymann, M. Morari, A. Zbinden and T. Schnider.
“Modeling and Closed-Loop Control of Hypnosis by Means of Bispectral Index (BIS) with Isoflurane”.
IEEE Transactions on Biomedical Engineering. In press.

A. Gentilini, C. Schaniel, M. Morari, C. Bieniok, R. Wymann and T. Schneider.
“A New Paradigm for the Closed-Loop Intraoperative Administration of Analgesics in Humans”.
IEEE Transactions on Biomedical Engineering. Submitted for publication.

A. Gentilini and M. Morari.
“Challenges and Opportunities in Control of Biomedical Systems”. AIChE Journal. In press
Conference Papers

“Automation in Anesthesia”.

A. Gentilini, S. Alemdar, C. Frei, M. Morari.
“Time Frequency Representation of Electro Encephalogram (EEG) during experimental painful stimulations correlate with movement response under general anesthesia”.

A. Gentilini, M. Gerosa, C. Frei, T. Schneider, M. Morari.
“Pharmacokinetic Pharmacodynamic (PK-PD) modeling of Bispectral Index (BIS) with Isoflurane for closed loop control of depth of anesthesia”.

C. Schaniel, A. Gentilini, M. Morari, C. Bieniok, R. Wymann and T. Schneider.
“Perioperative Closed-Loop Control of Analgesia in Humans”.

P. Grieder, A. Gentilini, M. Morari, C. Bieniok, R. Wymann and T. Schnider.
“A Patient Adaptive Approach for Closed-Loop Control of Bispectral Index (BIS) in Humans”.

A. Gentilini, M. Morari, C. Bieniok, R. Wymann and T. Schneider.
“Closed-loop Control of Analgesia in Humans”.

Talks

Invited seminar at the Institute of Process Engineering of ETH.
“Feedback control of hypnosis and analgesia in humans”.
Zürich, Switzerland, April 2001.

Invited seminar at Royal Victoria Hospital.
“Automation in Anesthesia”.
Montreal, Canada, March 2001.

Invited seminar at the Biomedical Engineering Department of McGill University.
“Automation in Anesthesia”.
Montreal, Canada, March 2001.

Invited lecture at Dräger’s GmbH Headquarters.
“Bispectral Index and Mean Arterial Pressure Controllers. A Challenge for Research and Development”.
Lübeck, Germany, January 2001.

Invited lecture at Pharsight Corporation Headquarters.
“Feedback Control of Hypnosis and Analgesia in Humans”.
Invited lecture at the École Polytechnique Fédérale de Lausanne.
“Automatic Control in Anesthesia”.
Lausanne, Switzerland, December 2000.

Presentation at the World Congress on Medical Physics and Biomedical Engineering.
“Closed-loop Control of Depth of Hypnosis during Anesthesia”.
Chicago IL, July 2000.

Presentation at the World Congress on Medical Physics and Biomedical Engineering.
“Time Frequency Representation of Electro Encephalogram (EEG) Correlate with Movement Response under General Anesthesia”.
Chicago IL, July 2000.

Invited lecture at the Politecnico di Milano.
“Controllori Automatici in Anestesia: un Nuovo Paradigma nelle Sale Operatorie”.

Invited lecture at Aspect Medical Systems, Inc.
“Automation in Anesthesia”.
Newton MA, April 2000.

Invited lecture at Roche Diagnostics Corporation.
“Automation in Anesthesia”.
Indianapolis IN, April 2000.

Presentation at the American Control Conference.
“Automation in Anesthesia”.

Presentation at the 18th Southern Biomedical Engineering Conference.
“Artifact Tolerant Controllers for Automatic Drug Delivery in Anesthesia”.

Presentation at the 18th Southern Biomedical Engineering Conference.
“Identification and Targeting Policies for Computer Controlled Infusion Pumps”.
References

Prof. Dr. Manfred Morari.
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University Hospital Balgrist.
Forchstrasse 340, CH-8008 Zürich.
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