1 Introduction

1.1 What Is Anesthesia

Anesthesia can be defined as a reversible pharmacological state where the patient's hypnosis, analgesia, and muscle relaxation are provided [24].

Hypnosis indicates loss of consciousness and absence of postoperative recall after surgery. Nowadays, hypnosis is measured through EEG derived parameters, such as spectral edge frequency (SEF), median frequency (MF), or bispectral index (BIS), which can be continuously recorded during operation. Among these measurement, nowadays BIS monitor is the most widely spread. In fact it is used in 40% of all Operating Rooms in the U.S., in 160 Countries on 12.2 million patients worldwide [3]. This technology relies on measuring the cortical brain activity of the patients by placing a sensor on the forehead of the patients. In this way the physicians obtain direct information about the effect of hypnotic agents and opioids. The EEG signal so recorded is then translated by the BIS monitor into a number ranging between 100 (indicating an awake patient) to zero (indicating the absence of brain electrical activity).

Analgesia is pain relief. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". This definition recognizes the interplay between the objective, physiologic sensory aspect of pain and its subjective, emotional, and psychological components.
As a consequence, up to now, there is no perioperative direct measurement of pain perception for an unconscious patient. An indirect measurement of pain perception can be extracted from the response of the patients to the application of external stimuli. The correlation between mean arterial blood pressure (MAP) and heart rate (HR) variations with stress response has been shown recently by Zanderigo et al. [95].
On the other hand, pain perception can be directly measured in conscious patients, through the Visual Analogue Score (VAS). The VAS is a measurement instrument, usually a horizontal line, 100 mm in length, anchored by word descriptors ("No pain" and "Very severe pain") at each end. The patients mark on the line the point that they feel represents their percep-

tion of their current state. The VAS score is determined by measuring in millimeters from the left hand end of the line to the point that the patient marks [26].

Muscle relaxation corresponds to inability to move, necessary to intubate the patient, to facilitate skin incision, and to repress involuntary movements response to external stimuli. The degree of relaxation of the patient is assessed through electrical stimulation of the ulnaris nerve in the wrist. Short electrical pulses are sent intermittently through the skin over a peripheral nerve while the contraction of a muscle supplied by that nerve is observed [40]. The patient is considered relaxed when no muscle contraction can be observed.

1.2 Motivation and Overview

In clinical practice, based on monitor readings and some patients specific target values, the anesthesiologists adjust the infusion rates of the hypnotic, of the analgesic, and of the muscle relaxant to maintain the vital parameters of the patients at an equilibrium state. In this sense, it is natural to associate his activity to the one of a feedback controller. Because of this analogy, in the last years the application of feedback control of anesthesia in clinical practice has been researched by several authors to help the anesthesiologists in his daily activity [35, 41, 44, 52, 55, 74, 53, 82]. Several benefits have been achieved through this application: improvement of the patients safety, decrease of the anesthesiologists work load, reduction of the incidence of side-effects in the post-operative phase and the hospitalization time after operation, capability of capturing inter-patient variability through controller tuning. In particular, within a time frame of seven years, our group developed model-based controllers for the automatic delivery of different anesthetic agents [18, 23, 24], opioids [24, 80], and muscle relaxants [80], which were successfully tested in the clinical practice.

Nowadays, because of the difficulty in obtaining the approval from the Food and Drug Administration (FDA) for the daily use of feedback controllers in

clinical practice, the interest in such devices has slightly decreased. Therefore, today's research in anesthesia is more focused on developing open-loop rather than closed-loop systems. In fact, model-based open-loop systems coupled with the newest monitoring techniques could provide the anesthesiologist with guidelines for optimal drug infusions [72, 85], while leaving him in complete control of dosing. Moreover, these systems could help rationally dose multiple drugs taking advantage of the arising synergies [49, 96] and allow the tuning of the infusion specifically for the patient. The ultimate advantage would be a reduction of the costs thanks to a reduced drug consumption and a shorter time spent by the patient in the post operative care unit. As a consequence, the identification and parameter estimation of the models describing drug distribution and effects play a decisive role in the development of such systems.
In this thesis we will show how the availability of the modeling knowledge can impact the daily life of the anesthesiologist, providing him with mathematical basis for optimal drug administration.
The issues we will investigate are presented in the following.

Optimal Drug Combinations

In Chapter 3, we will analyze the problem of how to optimally administer drug combinations. In fact, drugs are routinely combined in anesthesia and pain management to obtain an enhancement of the desired effects. However, a parallel enhancement of the undesired effects might take place as well, resulting in a limited therapeutic usefulness. Therefore, addressing the question of optimal drug combinations, one cannot avoid considering also side effects.
First, we will show how a search algorithm can be conveniently used in clinical practice for post-operative pain management to identify combinations of drugs providing adequate analgesia with low occurrence of side effects. Then, since the search algorithm cannot guarantee global optimality, in a second stage we will build a pharmacodynamic model describing the response surface resulting from the combinations of n drugs to exploit the problem of the uniqueness of the optimal patient's well-being point.

Chapter 3 is almost entirely based on:

[84] SVETICIC G., A. GENTILINI, U. EICHENBERGER, E. ZANDERIGO, V. SARTORI, M. LUGINBUEHL and M. CURATOLO: *Combinations of Bupivacaine, Fentanyl and Clonidine for lumbar epidural postoperative analgesia. A novel optimization procedure.* Anesthesiology 2004, 101:1381-1393.

[96] ZANDERIGO E., V. SARTORI, G. SVETICIC, T. BOUILLON, P.M. SCHUMACHER, M. MORARI and M. CURATOLO: *The Well-being model: A new drug interaction model for positive and negative effects.* Anesthesiology 2006, 104:742-53.

[97] ZANDERIGO E., V. SARTORI, G. SVETICIC, T. BOUILLON, P.M. SCHUMACHER, M. CURATOLO and M. MORARI: *A new model for drug interactions and optimal drug dosing.* In *IEEE Engineering in Medicine and Biology Society, Shanghai, China*, September 2005.

[67] SARTORI V., E. ZANDERIGO, G. SVETICIC, T. BOUILLON, P.M. SCHUMACHER, M. MORARI and M. CURATOLO: *The Well-being model: An application to the combination of intravenous morphine with ketamine.* Technical Report AUT05-07, Automatic Control Laboratory, ETHZ, Switzerland.

[69] SARTORI V., E. ZANDERIGO, G. SVETICIC, M. MORARI and M. CURATOLO: *Optimal drug dosing of morphine and ketamine in pain treatment.* In *International Society for the Study of Pain, Sidney, Australia*, August 2005.

[68] SARTORI V., E. ZANDERIGO, G. SVETICIC, M. MORARI and M. CURATOLO: *A novel procedure to estimate the interaction parameters between morphine and ketamine.* In *American Society of Anesthesiologists Annual Meeting, Atlanta, Georgia*, October 2005.

Real-time Individual Parameter Estimation

In Chapter 4 we will introduce the "Anesthesia Display", a novel advisory system which leaves the anesthesiologist in complete control of dosing but enables him to obtain real time information about the predicted drug concentrations and predicted combined effect in the patient resulting from his actions. The use of "population" parameters in the models describing drug distribution and effect implemented in the Anesthesia Display is complicated by the large inter-patients variability, which could result in a mismatch between the measurements displayed by the monitors and the estimation provided by the Anesthesia Display. As a consequence, the

physician will not trust the information of the Anesthesia Display and will discard its use. To overcome this problem, it is then necessary to adapt the model parameters according to the single patient's response.
Based on the measurement of hypnosis (BIS) and of the hypnotic infusion rates, we will develop an algorithm for the on-line individualization of some of the model parameters. Further, we will test this algorithm on data from a previous clinical study, to show how the parameters individualization can improve the prediction capabilities of the Anesthesia Display.

Chapter 4 is almost entirely based on:

[65] SARTORI V., P.M. SCHUMACHER, T. BOUILLON, M. LUGINBUEHL and M. MORARI: *On-line estimation of propofol pharmacodynamic parameters.* In *IEEE Engineering in Medicine and Biology Society, Shanghai, China*, September 2005.

[66] SARTORI V., P.M. SCHUMACHER, T. BOUILLON, M. LUGINBUEHL and M. MORARI: *Real-time individualization of propofol pharmacodynamic parameters.* In *American Society of Anesthesiologists Annual Meeting, Atlanta, Georgia*, October 2005.

[63] SARTORI V.: *On-line estimation of propofol pharmacodynamic parameters,* 2005. Diploma Project at the seminar for Statistic at ETH Zurich.

Optimal Pharmacokinetic Experimental Design

In Chapter 5 we will analyze the problem of optimal parameter estimation for pharmacokinetic models. In fact, mammillary pharmacokinetic models are widely used to design open-loop system for the automatic delivery of drugs during general anesthesia, i.e., Target Controlled Infusion (TCI) pumps. These models are estimated during ad hoc studies based on the administered dose and the only available measurement, the plasma concentration of the infused drug. It has been shown previously that the method of administration and the sampling frequency could affect the quality of the parameter estimation [4, 70]. When implementing the pharmacokinetic model in TCI systems, a poor estimation of its parameters could result in overdosing the patients [4], therefore threatening his safety.
The aim of this investigation is to extract guidelines for an optimal setup of pharmacokinetic experiment, to identify under which condition one can

obtain minimal variance estimation of the model parameters.

Chapter 5 is almost entirely based on:

[64] SARTORI V., T. KREJCIE, M.J. AVRAM and M. MORARI: *Optimal design of pharmacokinetic experiments.* Technical Report AUT06-01, Automatic Control Laboratory, ETHZ, Switzerland, 2006.

2 General Concepts