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Introduction

1.1 Optimal Analgesics Administration

This thesis aims at improving analgesics administration in clinical practice by defining criteria for the identification optimal analgesics dosing under different scenarios. Optimal dosing of analgesics is defined as the administration that allows the anesthesiologist to achieve and maintain an adequate analgesic effect for the patient while at the same time minimizing risks for the patient and costs for the hospital.

Analgesics misdosing leads to increased risks for the patient both in case of underdosing and overdosing. According to the American Society of Anesthesiologists, underdosing of analgesics leads to inadequate pain relief, that might lead to patient discomfort, injury because of lack of cooperation or adverse physiologic response to stress [4]. On the other hand, drug overdosing is in general associated with an increased incidence of side effects. Depending on the setting and the drug used, side effects of analgesics can range from, for example, motor block, nausea or sedation during postoperative care to ventilatory depression in case of conscious sedation. In this last case the drug's side effect represents a primary cause of morbidity for the procedure [4]. Side effects are not only risky for the patient, but they also represent a source of cost for the hospital that has to manage them. In addition, intraoperative drug overdosing is the most frequent cause of delayed emergence from anesthesia [96]. The administration of too elevated drug amounts prolongs the time the patient has to spend in the postoperative care unit to eliminate the drug in excess. Apart from being unpleasant for the patient, hospitalization time also represents a critical factor in the hospital's budget.

Therefore, optimal analgesics administration should provide an adequate level of analgesia while at the same time minimizing side effects and drug consumption. In this way, both the risks for the patient and the costs for the hospital are minimized. In clinical practice, pain relief plays a key role both intraoperatively, to reduce pain and discomfort associated with the surgical procedure, and postoperatively, to provide pain relief after the invasive surgery. Depending on the clinical setting, the identification of the optimal analgesics dosing presents different challenges. In this thesis

we focus on improving analgesics administration in three major clinical scenarios: postoperative care, conscious sedation and general anesthesia.

1.2 Optimal Analgesics Administration in Postoperative Care

The postoperative care unit is the unit dedicated to recovering from anesthesia, minimizing postoperative complications and providing pain relief to the patient after the invasive surgery. Usually, because of the strong postoperative pain, more than one analgesic drug are administered at the same time to take advantage of a potential synergism. On the other hand, the combination of more drugs might at the same time lead to a parallel enhancement of the undesired effects. The presence of multiple variables, such as drug concentrations, mode of administration or time interval between doses, results in hundreds of possible combinations that cannot be analyzed in any trial. Standard practice consists in dosing the analgesics based on clinical experience or trial and error. However, this might potentially result in a sub-optimal treatment.

In this setting, the challenge is to identify which administration leads to the highest pain relief with the lowest amount of side effects, under the constraint of testing only a few variants on the patient. In this thesis, we present two different successful approaches to solve the problem and show how these can be applied to improve postoperative treatment in clinical practice.

The first approach consists in the development of a novel *black-box optimization procedure*. Thanks to its novel structure, the proposed procedure allows for a straightforward identification of optimal combinations in clinical practice. The procedure is tested in a clinical study to optimize combinations of three analgesic drugs for lumbar epidural analgesia. The method proves successful in identifying combinations providing high analgesia with a limited amount of side effects after few steps.

Although representing an improvement with respect to standard practice, the proposed procedure presents the limitation of not providing any guarantee of global optimality. To address this issue, we undertake a second approach consisting in the development of a *new model for drug interactions*. By including for the first time the limitations imposed by the drug's negative effects into the expression of a global outcome parameter, the patient's well-being, the new model allows for a direct, analytical computation of optimal dosing for the combination of two or more drugs. Although the implementation is more complicated compared with the black-box approach, the modelling approach presents three major advantages. First it allows us to address the issue of global optimality, supporting from a theoretical point of view the application of the black-box optimization method to the combination of two drugs. Further, it creates a new framework to analyze the behavior of drug combinations under different conditions of synergistic or antagonistic interactions. Third, it allows us to derive general guidelines for optimal drug dosing. The model is estimated for the clinically relevant combination of morphine with ketamine.

1.3 Optimal Analgesics Administration in Conscious Sedation

Conscious sedation is a state of sedation where the patient retains the ability to breath spontaneously. Often, conscious sedation is performed administering opioids. However, opioids are known to induce a dose-dependent respiratory depression that is recognized as a primary cause of morbidity [4] in conscious sedation procedures. In this setting, the identification of the exact amount of drug to be administered in order to provide adequate analgesia while preserving the spontaneous ventilatory drive in the patient is an extremely critical issue. The scenario is further complicated by the extreme inter-patient variability in drug's sensitivity. This makes the dosing based on experience or population averages extremely ineffective.

From the point of view of a control engineer, the role of the anesthesiologist can be regarded, in some sense, as the role of manual feedback controller.

Based on monitor readings and measurements, the anesthesiologist doses the drug to achieve and maintain stable patient's conditions. Over the last decade, the idea of introducing automatic control for optimal drug delivery has received a lot of attention from the research community [31, 44, 45, 87, 60, 97, 102, 113, 114, 121, 122, 123, 129]. The goal of the controller in the surgical setting is to take over and/or improve parts of the complex process managed by the anesthesiologist. The ultimate advantages are increased patient safety and optimal drug administration. Automatic control would increase the safety level for the patient by taking over routine tasks allowing the anesthesiologist to concentrate on critical issues. Optimal dosing is achieved as the controller is programmed to tailor drug administration on individual response, administering the minimal amount of drug required to achieve and maintain the predefined goal. In recent studies, automatic control has been found to outperform manual control in maintaining the target signal at the predefined level, avoiding phases of inadequate control and shortening recovery times [81, 131].

Therefore, one spontaneous solution to the problem encountered during opioid administration in conscious sedation would be to automatically regulate drug administration based on ventilation measurements. However, for several reasons that are later illustrated in detail, a ventilation-based regulation of drug infusion is not feasible. Taking advantage of recently developed sensors for transcutaneous CO_2 measurements, the aim of this thesis is to explore the innovative idea of achieving optimal drug dosing in conscious sedation using CO_2 body content as a surrogate measurement for ventilation. We do this by designing an *automatic control system for drug dosing* based on the novel CO_2 sensors. The aim of the controller is to administer the optimal amount of drug to induce conscious sedation but maintain spontaneous ventilation, according to individual sensitivity and despite external surgical stimulation and disturbances. In order to design the controller, acquaintance with the complex physiological mechanisms involved in the human ventilatory system and of their dependence on drug administration is required.

Intensive research has been performed on mathematical modelling of the human ventilatory system. However, the state of the art model presents major drawbacks that considerably limit its applicability for our purposes.

Therefore, in this thesis, we develop a *new model* for the human ventilatory system in presence of ventilatory depressants. The new model captures the complex behavior of the system with a parsimonious structure, requiring a minimal number of parameters. In this way, the model allows for a direct identification of model parameters from experimental data. The model proves able to reliably reproduce the pharmacologic ventilation-depressive effect of three major drugs used in conscious sedation procedures.

After estimating model parameters for the widely used drug remifentanil, the new model is implemented as a patient simulator for controller design. We test the feedback system in simulations under different experimental conditions and varying individual sensitivities to the drug. The system shows good performance in tailoring drug infusion to the patient's needs to keep a pre-defined level of CO_2 in the body of the patient, rejecting external disturbances and painful stimuli.

1.4 Optimal Analgesics Administration in General Anesthesia

Analgesia is a fundamental component of general anesthesia, together with *muscle relaxation*, induced to facilitate the access to internal organs, and *hypnosis*, induced to achieve unconsciousness and absence of post operative recall. Following the idea of introducing automatic control to anesthesia management, several studies have been published on automatic control of hypnosis [44, 121, 122, 123] and muscle relaxation [87, 113, 114, 129] over the past decade. Conversely, the major issue of controlling patient's analgesia is still open.

The major challenge we are facing today for the control of adequate analgesia and, in general, for the definition of optimal analgesics administration during general anesthesia is the lack of a specific sensor for the analgesic level of the unconscious patient. No optimal administration can be defined if the final outcome is not measurable. At this stage, intraoperative analgesics administration during general anesthesia is not directly related to

pain treatment [58] and it may even be not proper to define pain perception when the subject is unconscious [106]. However, even the unconscious body reacts in different ways to the painful surgical stimulation. Typical reactions include for example pupil widening, increase of heart rate and blood pressure, contraction of skin vessels. The set of observed reactions induced by stressful stimulation is referred to as *stress response* of the body. Currently the stress response is used as guideline for intraoperative analgesics dosing [10, 71].

Thus, one natural approach to overcome the problem of measuring analgesia in the unconscious patient, is to search for changes induced by the stress response in the vital parameters that might be used as surrogate measurements for the experienced pain. In this thesis we undertake a first step in this direction, analyzing data from a volunteer study. The volunteer study is designed to investigate the reaction of several clinical end-points to experimental painful stimuli and the effect of the hypnotic isoflurane and the analgesics alfentanil on those end-points.

Mean arterial blood pressure (MAP) variations is particularly influenced by painful stimulation. However, in the standard surgical setting, MAP is acquired non-continuously with a relatively high sampling time, generating a lack of relevant information about the fast MAP changes induced by the painful surgical stimulation. Analyzing the volunteer study data, we are able to relate the fast, stress-induced MAP variations to the stress-induced variations in HR. This allow us to develop a procedure to non-invasively obtain a continuous real-time MAP estimate based on HR, a routinely available signal. The major advantage of the proposed procedure is that it provides the anesthesiologist with detailed information about the vital state of the patient without requiring additional sensors and being robust to inter-patient variability.

However, MAP might be influenced by a variety of confounding factors. Therefore, basing analgesics infusion only on the MAP signal is unfeasible. Major improvement might be achieved by taking into account other physiological signals containing additional information about the patient's stress level. According to clinical experience and to recent literature [84], the amplitude of the pulse wave signal (PWA) seems to be sensitive to the degree of

the experienced painful stimulation. However, no specific studies assessing whether PWA is significantly influenced by pain and how analgesic drugs affect this phenomenon are available, so far. To assess the dependency of PWA from different potential factors, we make use of statistical techniques to analyze the PWA signals of volunteers under anesthesia subject to painful stimulation. PWA proves to react significantly to painful stimulation, the extent of the reaction being influenced by analgesic drugs, volunteers sensitivity and fatigue. The performed analysis supports the hypothesis that PWA might significantly indicate the occurrence of a stressful event in the unconscious patient.

However, MAP and PWA are only two among the large number of clinical end-points monitored during surgery. The standard clinical setting provides, for example, information about heart rate, blood pressure, pulse wave, electroencephalogram and electromyography parameters. Based on its experience, the anesthesiologist is able to obtain a description of the overall analgesic state of the patient by extracting the key information from the large amount of data available. In order to formulate a more rigorous, mathematical description of this experience-based procedure, in this thesis, we make use of multivariate statistical techniques to identify the principal sources of information among the large amount of available data. The analysis performed allows us to show that a subset of the acquired parameters exists, which accounts for the major part of the pain-induced variability and that the composition of the relevant subset is influenced by the administered drugs, which depress the importance of certain signals consistently with clinical experience.