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Automation of the anesthetic process: new computer-based solutions to deal with the current frontiers in the assessment, modeling and control of anesthesia

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AUTORIZAN

A la defensa de la Tesis Doctoral titulada "*Automation of the anesthetic process: new computer-based solutions to deal with the current frontiers in the assessment, modeling and control of anesthesia*", realizada por D. José Manuel González Cava, bajo nuestra dirección y supervisión, y que presenta para la obtención del grado de Doctor por la Universidad de La Laguna.

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Abstract

The current trend in automating the anesthetic process focuses on developing a system for fully controlling the different variables involved in anesthesia. To this end, several challenges need to be addressed first. The main objective of this thesis is to propose new solutions that provide answers to the current problems in the field of *assessing*, *modeling* and *controlling* the anesthetic process.

Undoubtedly, the main handicap to the development of a comprehensive proposal lies in the absence of a reliable measure of analgesia. This thesis proposes a novel fuzzy-logic-based scheme to evaluate the impact of including a new variable in a decision-making process. This scheme is validated by way of a preliminary analysis of the Analgesia Nociception Index (ANI) monitor on analgesic drug titration.

Furthermore, the capacity of the ANI monitor to provide information to replicate the decisions of the experts in different clinical situations is studied. To this end, different artificial intelligence-based algorithms are used: specifically, the suitability of this index is evaluated against other variables commonly used in clinical practice.

Regarding the modeling of anesthesia, this thesis presents an adaptive model that allows characterizing the pharmacological interaction effects between the hypnotic and analgesic drug on the depth of hypnosis. In addition, the proposed model takes into account both inter- and intra-patient variabilities observed in the response of the subjects.

Finally, this work presents the synthesis of a robust optimal PID controller for regulating the depth of hypnosis by considering the effect of the uncertainties derived from the patient's pharmacological response. Moreover, a study is conducted on the limitations introduced when using a PID controller versus the development of higher order solutions under the same clinical and technical considerations.

Keywords: Analgesia assessment; Artificial intelligence; Automation of anesthesia; Closed-loop anesthesia; PK-PD modeling; Robust optimal control.

Resumen

La tendencia actual en la automatización del proceso anestésico se centra en el desarrollo de un sistema para el control integral de las distintas variables involucradas en anestesia. Para ello, sin embargo, es necesario hacer frente a una serie de retos. El principal objetivo de esta tesis es proponer nuevas soluciones que den respuesta a los problemas actuales en el ámbito de la *evaluación*, *modelado* y *control* del proceso anestésico.

Sin duda, el principal hándicap para el desarrollo de una propuesta integral radica en la ausencia de una medida fiable del nivel de analgesia. Este trabajo propone un esquema novedoso basado en lógica difusa que permite evaluar el impacto de incluir una nueva variable en la toma de decisiones. Para su validación, se realiza un análisis preliminar del monitor Analgesia Nociception Index (ANI) en la dosificación de analgésico.

En un segundo estudio, se analiza la capacidad del ANI para proveer información que permita replicar las decisiones de los expertos en distintas situaciones clínicas. Para ello, se emplean algoritmos basados en inteligencia artificial. En concreto, se evalúa la validez de este índice frente al uso de otras variables empleadas en la práctica convencional.

En el ámbito del modelado, esta tesis presenta un modelo adaptativo que permite caracterizar los efectos de las interacciones farmacológicas entre el fármaco hipnótico y analgésico sobre el nivel de profundidad hipnótica del paciente. Asimismo, el modelo propuesto tiene en cuenta las variabilidades inter e intrapaciente observadas en la respuesta del sujeto.

Por último, teniendo en cuenta el efecto de las incertidumbres derivadas de la respuesta farmacológica del paciente, este trabajo presenta la síntesis de un controlador PID óptimo robusto para la regulación del nivel de hipnosis. Además, se lleva a cabo un estudio sobre las limitaciones introducidas al hacer uso de un controlador PID frente al desarrollo de soluciones de orden superior bajo las mismas consideraciones clínicas y técnicas.

Palabras clave: Automatización del proceso anestésico; Control en lazo cerrado; Control óptimo robusto; Evaluación de analgesia; Inteligencia artificial; Modelado PK-PD.

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1. Introduction

1.1. Motivation

Advances in engineering methods and the increase in computational power have resulted in high-performance real applications in several fields. Particularly, this has led to great progress in medicine, such as the development of novel medical devices, the design of new applications to assist in different decision-making process, and the creation of new systems for managing resources. Nowadays, medicine and engineering go hand in hand to solve the problems of society. Among the different engineering disciplines, control engineering is highly relevant in many clinical applications. Beyond the traditional use of this technology for the self-regulation of clinical devices, control engineering has emerged as a useful tool for both modeling and treatment tasks. These applications include, for instance, the balance control systems in Parkinson's disease [1]–[3], or the administration and dosage optimization of drugs for diabetes and control of blood glucose [4]–[6]. However, the automatic control of the anesthetic process has definitely emerged as the clinical discipline in which control engineering has had the greatest relevance so far.

The development of new medical devices for monitoring, the availability of improved drugs and the training of a greater number of anesthesiologists are evidence of the increased safety of anesthesia [7]. In recent decades, the mortality rate from anesthesia has been estimated at 1 in 250,000 [8]. Some factors related to patient habits such as smoking, obesity, alcoholism or the failure to control hypertension, diabetes mellitus or asthma have been correlated with an increased risk during anesthesia. But the role of human error in morbidity and mortality must be also considered when analyzing the potential risks in anesthesia. During the process, the anesthesiologists must manage different tasks simultaneously. The activity of the anesthesia providers involves observation, decision-making, action and evaluation. The experts have to interpret key findings during the intervention, weighing the most recent information and adapting the criteria as the process evolves. Sometimes, the anesthesiologist may become overwhelmed by the amount of information involved in the process. In addition, other factors, like sleep loss or fatigue, degrade work performance. Dealing with these factors requires the development of new methodologies and decision support tools to aid the experts in the operating

room, so that they can manage the information easily and focus on the most relevant factors during the clinical process.

The objective of closed-loop anesthesia is to supply different drugs to ensure an optimal depth of anesthesia (DoA) during surgery. Specifically, the control of DoA involves providing the appropriate depth of hypnosis (DoH), analgesia, and neuromuscular blockade. The introduction of a closed-loop strategy for drug titration allows the anesthesiologist to focus on higher-level tasks, minimizing deviations in the drug titration protocol coming from individual criteria and improving the overall performance of the anesthetic process. Closed-loop anesthesia is not a new concept. In the 1950s, Single et al. proposed an initial design based on the automation of drug administration during anesthesia [9]. Unlike the automation of most industrial processes, controllers for anesthesia were difficult to design and implement due to the lack of knowledge behind the physiological process, together with the uncertainty in the systems involved [10]. Nowadays, the progress made toward developing new control strategies, together with an improved insight into the pharmacological process, have led to the development of a wide number of proposals [11].

Relevant benefits have been observed when applying closed-loop strategies in anesthesia. Previous studies have concluded that the use of closed-loop schemes improve patient safety, reducing the workload of anesthesiologists while making more efficient use of resources [12]. This has spurred new research to deal with the current challenges in the automation of anesthesia. New advances toward the *total* control of the anesthetic process will lead to important technical, economic, and social benefits by:

- Increasing patient safety due to a more personalized drug titration procedure, improving postoperative recovery, and reducing patient recovery time.
- Allowing the anesthesiologist to focus on relevant functions, reducing the time spent in repetitive low-level tasks, and assuming a supervisory role to manage potential complications during the process.
- Optimizing the use of clinical resources, ensuring accurate drug consumption, and reducing the time spent in post-anesthesia care units.

- Promoting the digitization of the anesthetic process, recording the information derived from patient monitoring to improve the clinical evaluation and the post-operative analysis.

1.1.1. Problem statement

The closed-loop control of anesthesia comprises three main challenges:

i. The *assessment* of the anesthetic state. This includes an accurate evaluation of the depth of hypnosis, analgesia and neuromuscular blockade to make appropriate control decisions.
ii. The design of mathematical *models* to represent the effect of the drugs on the different variables involved. The more reliable the model, the better adjusted the controller that can be proposed.
iii. The design of *controllers* adapted to the main features of the process. This must include a robust response to deal with variabilities in patients' responses.

It is, therefore, a sequential process in which the success of each stage is highly dependent on the state of the previous one. This fact explains the unbalanced advances found when automating the different variables involved in the anesthetic process. While a large number of proposals for controlling the DoH can be found in the literature, only a few solutions for dealing with the automation of analgesia have been proposed.

The lack of a measure to quantify the analgesic state of patients during general anesthesia has held back proposals for accurate models, and thus the development of reliable closed-loop solutions [13]. The intraoperative evaluation of analgesia has traditionally been based on heart rate and arterial pressure fluctuations; however, neither of these parameters is specific for monitoring analgesia [14]. Therefore, this problem not only affects the automation of the anesthetic process, but also the whole clinical decision-making process, since no reliable method for intraoperative analgesia monitoring has been presented so far. This results in undesirable clinical consequences. According to the US Institute of Medicine, 80% of patients who undergo surgeries report postoperative pain, even reaching extreme pain levels [15]. Inadequate levels of analgesia in patients undergoing surgery may result in risk of overdosing, risk of post-operative hyperalgesia, and it may increase recovery time after the surgery [16]. In

addition, the presence of acute pain during surgery has been related to the development of chronic pain [17].

New measures based on the analysis of different physiological variables to quantify the level of analgesia during general anesthesia have been researched. These indexes are intended to make an indirect measurement of autonomic nervous system (ANS) activity. Many of these measures have led to new commercial devices to characterize the nociception-anti-nociception balance during anesthesia. The Analgesia Nociception Index (ANI), developed by Mdoloris Medical Systems, has been tried in clinical practice. Some studies concluded that the ANI monitor may detect the effect of painful stimuli and could be correlated with the postoperative pain reported by patients. However, these studies have shown no evidence of decisive results that can be considered of current clinical relevance [18], [19]. Furthermore, the methodology used to test the suitability of these new monitors in clinical practice is debatable. As a result, unless further studies investigate their clinical applicability, these monitors are not yet optimized for use in daily clinical routines.

This is the main current handicap to the development of a strategy toward the *total* automation of the anesthetic process, but not the only one. Taking into account the variables involved in the anesthetic process, a multi-input multi-output (MIMO) strategy must be proposed that simultaneously controls hypnosis, analgesia and neuromuscular blockade. Although the proposal of single-input single-output (SISO) controllers for the individual variables has been widely researched, the development of a new MIMO structure for anesthesia must include new, relevant aspects. On the one hand, the possible couplings that may exist between the different control loops derived from drug interactions must be considered. Specifically, pharmacological interactions between hypnotic and analgesic drugs on the DoH have been reported [20]. Thus, merging the control of both analgesia and DoH variables simultaneously will make it necessary to analyze possible drug interactions to optimize the performance of the strategy. However, there are several factors that turn this analysis into a challenge. First, the variability observed in the patients' response to the drugs, known as interpatient variability, requires an individualized approach [21]. In addition, some other studies highlight that intrapatient variability is another major aspect to consider when modeling the anesthetic process [22]. This implies variations in the patient's response throughout the surgery.

As a result, a reliable adaptive model to represent the pharmacological interactions between the different variables involved in the anesthetic process will be required before a closed-loop scheme for the total control of anesthesia can be developed.

On the other hand, a suitable controller algorithm to be included in the MIMO structure for each variable involved in the closed-loop strategy should be proposed. This involves not only the proposal of the control algorithm, but also the definition of all those clinical factors likely to affect the performance of the solution. Research efforts have focused mostly on the development of SISO controllers for the DoH. Several algorithms have been proposed, from PID controllers to more sophisticated strategies, such as fuzzy-logic controllers, model predictive control (MPC) or artificial intelligence-based algorithms [23]. Regardless the algorithm used, interpatient variability emerges as a limiting factor in the performance of closed-loop strategies [24]. Recent research has focused on developing robust strategies to deal with uncertainty in the patients' response. These studies have resulted several controller algorithms being proposed. PID robust controllers have been widely researched in this discipline due to their simplicity and the successful results obtained in clinical validations. However, new proposals based on more complex strategies are constantly emerging. As a result, a comparison to determine the real benefits when using a higher-order robust controller versus a PID robust controller must be conducted. Establishing a fair comparison between the controller types found in the literature is not straightforward. The design objectives commonly vary between published studies, and they are not always explicitly stated in works presenting manually tuned controllers. Furthermore, the sets of patient models used for controller synthesis vary across research groups, as do the dynamics used to evaluate the resulting controllers. Thus, in order to make a meaningful comparison between controller types, measures of performance and robustness to deal with clinical demands must be standardized.

1.2. Scope

Regarding the current problems in automating the anesthetic process, the main motivation behind the work that resulted in this thesis was to make new contributions to clarify current questions involving the three main challenges in closed-loop anesthesia: *assessment*, *modeling* and *control*.

First, this thesis aims to provide a new insight into analgesia monitoring as a prior step towards the future development of a strategy for the total control of the anesthetic process. Specifically, considering the state of the art, the proposal of a new perspective for analyzing the ANI index as a tool for analgesia monitoring is intended. To this end, it will be necessary to study the usefulness of introducing the ANI index as a feedback variable to guide the drug infusion. This includes the proposal of a novel methodology to introduce new variables in a decision-making process. This methodology will also allow the analysis of the ANI as a guidance variable to replicate the decisions made by an anesthesiologist during surgery. Advances in this sense would give rise to the development of closed-loop strategies based on the information displayed by the ANI for the dosage of analgesic.

Furthermore, the current trend evidences that the next step toward the total control of the anesthetic process will lie in the integration of individual closed-loop controllers in a MIMO structure. Thus, the pharmacological interactions between drugs makes it necessary to develop new models capable of replicating drug interactions before a structure for fully controlling anesthesia is designed. These models must take into account all the relevant factors that may condition the performance of the control strategy, including the uncertainties introduced by the different systems involved in the anesthetic process. In particular, this thesis aims to propose a new methodology to model the depth of hypnosis during general anesthesia as a preliminary step for designing a total closed-loop strategy for anesthesia.

Finally, the proposal of a controller structure to deal with each variable involved in anesthesia is not trivial. Considering the main features of the anesthetic process, this thesis will propose the design of a robust controller for the DoH to deal with the uncertainty introduced by interpatient variability. In addition, the large number of alternatives presented for controlling the DoH makes it necessary to analyze the real benefits when using a high-order controller versus a simpler structure. This thesis will compare the performance achieved by a robust optimal filtered PID controller with a robust optimal higher-order LTI controller. For fairness of comparison, this analysis will be based on the evaluation of the same control objective, constraints, and clinical considerations. The main conclusions of this study will be applicable to future developments, providing new information to be considered in the design process

intended to yield a proposal for the individual controller of DoH to be included in the scheme for the total control of anesthesia.

The answer to the above questions would have an impact on the progress made toward the total automation of the anesthetic process. From the technical point of view, it would involve:

i. Validating a new clinical parameter to be used as a feedback variable in the decision-making process for the analgesia assessment. Initially, this would lead to the development of a decision support system for the clinician that, after the clinical validation, could result in a closed-loop structure for the automation of analgesia.
ii. Developing a new methodology to model drug interactions during anesthesia. This will be required before a reliable MIMO structure can be proposed.
iii. New research focused not only on proposing a control strategy for closed-loop analgesia, but also on shining a new light on the current challenges, including analyzing the main factors and limitations for closed-loop control of the DoH.

Undoubtedly, this would imply great advances that will motivate the development of a MIMO strategy toward the total control of the anesthetic process. From a clinical perspective, the formalization of a novel scheme to introduce a new clinical variable in the decision-making process could be extrapolated to other variables. Likewise, the study of the ANI monitor as a guiding variable for analgesia assessment, together with a new model for drug interactions, and the identification of the main factors likely to affect the drug delivery process, could yield new clinical knowledge to optimize the effect of the drugs on patients undergoing general anesthesia. In short, this work will deal with the current challenges in closed-loop anesthesia involving the total automation of the anesthetic process. This would lead to the improved use of both human and material resources, as well as to increased patient safety during general anesthesia.

1.3. General anesthesia overview

According to the American Society of Anesthesiologists, "*General anesthesia is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation*" [25]. Unlike other types of anesthesia, such as moderate sedation, local or regional anesthesia, general anesthesia is preferred when a long or complex surgery is expected. Specifically, general anesthesia implies the induction of a balanced state of unconsciousness, including the absence of pain sensation and neuromuscular blockade to facilitate endotracheal intubation and improve surgical conditions. To this end, different drugs are delivered simultaneously to ensure an adequate level of anesthesia, avoiding dangerous situations for the patient. An important task of the anesthesiologist consists of evaluating the current anesthetic state of the patient so as to supply the proper drug dosage based on their real needs. As a result, different clinical variables for assessing the hypnosis, analgesia and neuromuscular blockade must be monitored continuously during the surgery.

1.3.1. Variables involved in the anesthetic process

According to the above definition of anesthesia, a lack of sensation, nociceptive blockade and immobility are the goals of general anesthesia. A combination of hypnotic, analgesic and muscle-relaxant drugs must be delivered to ensure the appropriate conditions for the surgery. To this end, each variable must be measured to adjust the drug delivery accordingly. The clinical variables involved, as well as the main drugs and monitors commonly used in the anesthetic process, are presented below.

Hypnosis

Different definitions of hypnosis can be found in the literature. The American Psychological Association (APA) defines hypnosis as "*a state of consciousness involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion*" [26]. In anesthesia, hypnosis consists of suppressing the experience of surgery by suppressing consciousness or ensuring disconnection [27]. This is the result of delivering hypnotic drugs during the clinical process to induce unresponsiveness and amnesia. Propofol is

probably the most frequently administered intravenous drug for hypnosis [28]. Using propofol in general anesthesia has resulted in favorable operating conditions and rapid recovery [29].

Physically, the hypnotic drugs hyperpolarize neurons by increasing inhibition and altering neuronal activity [30]. The effects can be observed in the electrical activity of the brain through the electroencephalogram (EEG). Variations in frequency and amplitude in the EEG signal have been demonstrated to be correlated with the hypnotic state of the patient [31]. Specifically, an alpha predominant activity has been observed in the EEG during general anesthesia. Although raw EEG data presents complete information to evaluate the changes in the brain activity, interpreting these variations from the unprocessed EEG in real time is challenging. Clinicians prefer to use electroencephalogram-based indexes for monitoring the depth of anesthesia. Time domain derived indexes have been proposed for analyzing the EEG; however, the spectral analysis seems to be more practical and informative, considering the raw signal [32]. Specifically, the bispectral analysis is an advanced technique that quantifies the degree of phase coupling among the frequency components of a signal [33].

Different monitors have been developed for anesthesia that rely on analyzing the raw EEG. Among all the available options, the bispectral index (BIS) has been widely used in clinical practice. The algorithm implemented in the monitor was developed by Aspect Medical Systems. The BIS is a dimensionless parameter synthesized from the EEG that provides quantitative information from the DoH. This index ranges from 0 (isoelectric EEG) to 100 (fully awake patient). BIS values between 40 and 60 have been suggested for general anesthesia [34]. Several clinical trials conducted have evidenced the suitability of the BIS monitor for assessing hypnosis in general anesthesia [35].

Analgesia

Analgesia is related to pain relief. Pain can be defined as "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"* [36]. This definition evidences the importance of the subjective component affecting this variable. This psychological factor is minimized during general anesthesia. Nociception represents the neurophysiology component of pain to be controlled in the

anesthetic process [37]. Nociception implies the recognition and transmission of painful stimuli to the central nervous system (CNS). Nociceptors are peripheral afferent nerve endings capable of detecting tissue injury during the surgery [38]. This physiological process activates the ANS to cope with the alert detected by the nociceptors [39]. The ANS is divided into two major branches: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). While the SNS is responsible for "fight or flight" responses, the PNS oversees maintenance functions of the body, such as digestion [40]. Therefore, both SNS and PNS control different physiological process and organs that are essential to survival.

Main efforts for assessing analgesia have been focused on measuring ANS activity; however, the complexity of this physiological process is such that this challenge remains unsolved. Consequently, current proposals for measuring nociception during anesthesia rely on measuring indirect signs derived from the sympathetic-parasympathetic activity. Traditional protocols for delivering painkillers have been based on indirect signs, such as movement, presence of tachycardia, sweat or lacrimation [41]. Different studies claim the development of new indexes derived from indirect physiological variables correlated with nociception [42]: however, further research must be conducted to confirm the validity of these devices for monitoring nociception.

The most commonly used opioids for analgesia are morphine, fentanyl, sufentanil, alfentanil and remifentanil. Remifentanil has emerged as a popular drug for intravenous anesthesia as it achieves the peak effect relatively quickly [43]. Remifentanil is recommended when a rapid recovery is desirable or the opioid titration is unpredictable or difficult [44].

Neuromuscular blockade

Neuromuscular blocking agents are used in anesthesia to interrupt the transmission of nerve impulses, resulting in skeletal muscle relaxation [45]. Neuromuscular blockade is recommended to facilitate endotracheal intubation, optimizing surgical conditions, and assisting with mechanical ventilation in patients who have reduced lung compliance [46]. Unlike hypnosis or analgesia, monitoring depth of neuromuscular blockade is not a standard practice among clinicians during anesthesia. Recent studies revealed that objective assessment based on monitoring techniques is only used by a low percentage of anesthesiologists [47]. A

low accuracy in assessing neuromuscular blocking drugs produces side effects in patients as a consequence of residual drugs after surgery. Different methods for neuromuscular monitoring have been proposed, including clinical tests, qualitative and quantitative evaluations. Most of these rely on stimulating the peripheral nerve while evaluating the responses evoked [48]. There are different drug alternatives for neuromuscular blockade, depending on time-acting effect. Rocuronium is preferred in clinical practice for being fast acting, but some other options, like atracurium or vecuronium, are also widely used.

1.3.2. Stages of anesthesia

Regarding the temporal evolution of the surgery, the anesthetic process can be divided into three different stages, as described below.

Induction

Induction is a transient phase from an awake state to an adequately anesthetized state. To this end, an intravenous administration of drug is normally used to facilitate a rapid effect. A combination of a large dose of hypnotic (propofol) and analgesic (remifentanil) is commonly administered. Once an accurate depth of anesthesia is achieved, these bolus doses are followed by a constant infusion rate of the drugs. The neuromuscular blocking drug is also supplied in case a tracheal intubation is needed for direct laryngoscopy. The main aim during this phase is to achieve the appropriate level of anesthesia in terms of hypnosis, analgesia and muscular blockade in a short period, ensuring safe conditions to perform the surgery. However, an excess dose may result in overshooting the desired effect, causing some complications during the surgery or post-operative side effects. In addition, the effects of the drugs vary widely depending on individual factors such as age, gender, mass and height [49]. All these factors must be taken into account during the induction.

Maintenance

After induction, the effects of the drugs have to be maintained throughout the surgery. The different drugs must be co-administered to regulate the depth of hypnosis, analgesia and muscular blockade levels against external disturbances. Particularly, changes in hypnosis and

analgesia have been evidenced in response to noxious stimuli during surgery [50]. The proper dosage of drugs during the maintenance phase will depend on an accurate evaluation of the patient, as well as on the expertise of the clinician.

Emergence

Emergence from general anesthesia is a transitional phase, since the drug administration is ceased until the return to consciousness once the surgery finishes. Before halting the titration of hypnotics, the absence of skeletal muscle relaxation should be ensured to avoid anxious situations for the patient. Only analgesia needs to be continued to prevent pain in the recovery phase.

1.3.3. Techniques for drug titration in anesthesia

Different techniques are used to supply drugs during anesthesia. Regarding the means of administration, intravenous or inhaled anesthetics can be considered. Taking into account the decision-making scheme to adapt the infusion rates during surgery, manual administration, target-controlled infusion (TCI) or closed-loop schemes can be selected. A further description of the different techniques is presented below.

Inhalational anesthesia vs. total intravenous anesthesia

Inhaled drugs in anesthesia were first used in the 19th century. Nowadays, this process involves inhaling a volatile anesthetic or nitrous oxide to induce and maintain anesthesia. The drug is administered through a face mask, laryngeal mask or tracheal tube connected to a vaporizer [51]. The most common inhalational anesthetics are sevoflurane, desflurane and nitrous oxide. Inhaled anesthetics have been traditionally preferred for anesthesia due to their more precise control, as well as to their ample potency and rapid recovery times [52]. However, there exist several scenarios in which inhalational anesthesia has been contraindicated [53]. Alternatively, total intravenous anesthesia (TIVA) is a technique in which the induction and maintenance of general anesthesia relies upon intravenous agents. TIVA can be applied either with a single drug or any combination of hypnotics and opioids. The main advantages of TIVA include a better recovery profile, reduced risk of postoperative nausea and vomiting, and

preventing intraoperative wake-up [54]. The development of advanced pharmacokinetic and pharmacodynamic models for intravenous anesthesia has led to the increased use of TIVA in anesthesia. Nowadays, the use of TIVA or inhalational anesthesia mainly depends on the type of surgery and the patient's characteristics [55].

Manual administration

Manual administration has been traditionally used to deliver anesthetic agents during surgery. The decisions made include selecting the appropriate drug and dosage level, as determined by the morphological factors of the patient, age or type of surgery [24]. In general, the decisions made to adjust the drug dose during induction and maintenance are reactive. The clinician evaluates the current state, varies the infusion rate accordingly, and observes the results. This description of the manual process turns the anesthesiologist into a "human controller" in the loop. This condition results in intermittent and irregular control actions [56]. All the relevant variables should be monitored to guide the anesthetic process. The anesthesiologist must be aware of unexpected circumstances that may affect not only the state of the patient, but also the performance of the medical equipment in the operating room. The clinicians' decisions rely mainly on their experience and knowledge. The anesthesiologist has to be in charge of different simultaneous tasks, reducing the accuracy of the decisions made throughout the process. A schematic overview of the manual drug dosing is shown in Figure 1.1.

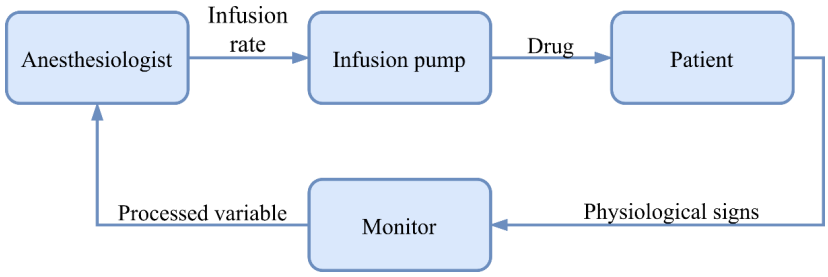

Figure 1.1. Schematic overview of manual drug dosing.

Target-controlled infusion

The main problem when administering drugs manually during anesthesia lies in the intermittent and irregular control actions, which reduce the general performance of the process. The first steps toward a more robust dosing protocol focused on automating the drug delivery. Target-controlled infusion is "*a technique of infusing intravenous drugs to achieve a user-defined predicted ("target") drug concentration in a specific body compartment or tissue of interest*" [57]. This technique, first performed in 1979 by Schüttler and Schwilden, is based on pharmacologic principles. A pharmacokinetic model is capable of simulating the drug concentration in the target effect-site concentration. The effect site relates the drug disposition (pharmacokinetics) and the drug effect (pharmacodynamics) observed in a specific variable [58]. Different models have been proposed in anesthesia to describe the effect of the different anesthetic drugs on a certain clinical variable [59], [60]. Some covariate factors such as weight, height or age can be included in the pharmacokinetic-pharmacodynamic (PK-PD) models. Unlike the manual infusion, instead of setting the infusion rate, the clinicians must set the target concentration aimed at the effect compartment. Along the anesthetic process, the clinician must evaluate the clinical effect on the controlled variable and change the target concentration accordingly. A schematic representation of the TCI system is shown in

Figure 1.2.

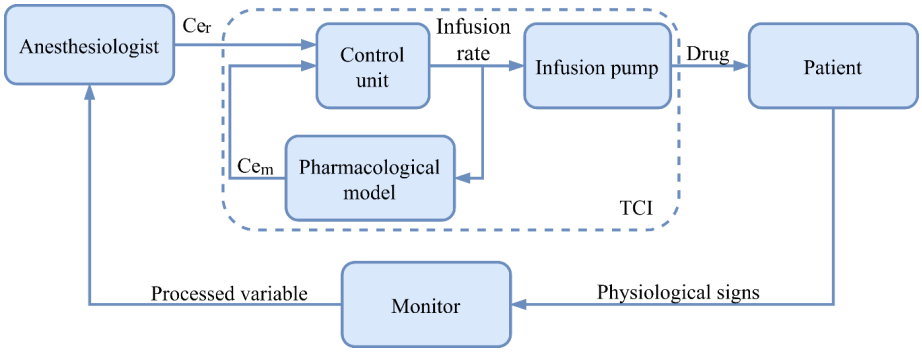

Figure 1.2. Schematic overview of a TCI system. Ce_r and Ce_m refer to the target and modelled effect-site concentrations, respectively.

In 1983, Schüttler et al. reported the first clinical results based on the CATIA (computer-assisted for total intravenous anesthesia) system [61]. In 1996, the Diprifusor module was commercialized for TCI propofol anesthesia [62]. This module ensured standardized drug delivery for any TCI device and was implemented in different commercial pumps such as Graseby, Alaris, Fresenius and Terumo. Open TCI systems based on different drugs and new PK-PD models were developed later [63]. Originally, the algorithms were designed to be run on a computer. Nowadays, a microprocessor installed in the infusion pump is capable of performing the calculations and control the dosage.

Although TCI systems have been widely used in the last two decades, several anomalies have been observed in clinical practice [64]. This technique relies on using models obtained from a large number of patients enrolled in different clinical studies. Despite this fact, some variance has been observed when applying these theoretical models to the population, not only variabilities between patients, but also variations in the response of the same patient throughout the surgery [65]. In addition, this system cannot detect the effect of external disturbances affecting the process. The main weakness of this technique lies in the open loop control scheme behind this strategy. As a result, the only way to include some feedback is to update the target-setting according on the observations of the clinicians. Further research should be conducted in this field to deal with the current problems.

Closed-loop infusion

The state of a patient undergoing general anesthesia must be evaluated to adapt the drug titration continuously. Although this practice is common in the manual infusion scheme, the automation of the drug dosage proposed by TCI relegates this feedback information to the background, in which the clinician must adjust the target concentration. In contrast with open loop control, closed-loop control does not require manual input. The concept of “closed-loop” on which most control strategies are based evidences the importance of considering a feedback variable for proper decision-making. This idea has turned the automatic control of anesthesia into a challenge for both clinicians and control engineers. The suitability of synthesizing a closed-loop controller has motivated the development of several ad-hoc strategies to deal with this problem. The goal when designing closed-loop controllers in anesthesia is rapid induction

while limiting the undershoot. During the maintenance phase, the controller must keep the patient at an adequate level of anesthesia, rejecting any disturbance likely to alter the optimal conditions for the surgery [66]. An example of a typical closed-loop scheme for controlling clinical variables during anesthesia is shown in Figure 1.3. The main aim of this strategy is not to replace the anesthesiologists, but to allow them to focus on higher-level tasks.

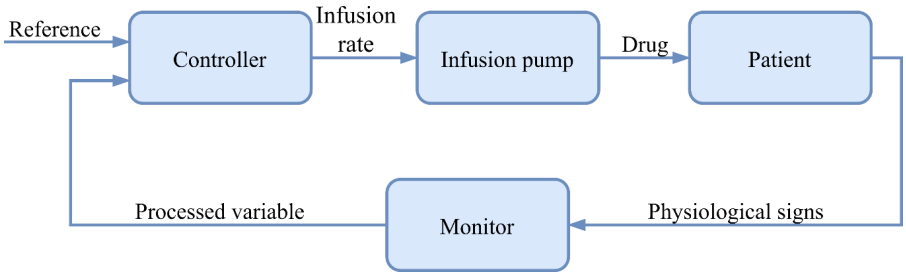

Figure 1.3. Closed-loop scheme for the control of a clinical variable in anesthesia.

Over the last decades, the availability of clinical devices for monitoring the anesthetic state of the patients, together with the development of mathematical models capable of simulating their clinical response, have led to the proposal of different closed-loop strategies. It is precisely these two conditions that have led to advances in the control of hypnosis compared to the control of analgesia. In the 1950s, the first clinical studies to analyze the feasibility of closed-loop controllers in anesthesia were carried out [9]. Recently, different PID, MPC and fuzzy based-proposals have evidenced an improvement in the performance of the hypnotic process management compared to the manual process [67]–[69].

1.4. Control strategies in anesthesia

The automation of the anesthetic process arises from the need to free the anesthesiologist from low-level repetitive tasks. In this sense, making regular decisions adapted to the real anesthetic state of the patient can be ensured throughout the surgery. The availability of reliable measures to quantify both DoH and neuromuscular blockade, together with a knowledge of the physiological system behind the process, have led to the development of accurate models. Many of these models have been based on compartmental PK-PD structures [70]. Artificial

intelligence techniques have also been used to propose intelligent models [71]. The evolution of these techniques has had an impact on the development of new control strategies that are capable of yielding successful results in clinical scenarios. However, the absence of a metric that is capable of accurately quantifying the depth of analgesia during the anesthetic process has hindered the proposal of accurate models, and therefore of reliable closed-loop solutions. To address this drawback, only partial strategies have been intended so far. As a result, the potential of closed-loop control of analgesia has not been exploited yet. In keeping with the scope of this thesis, an analysis of the evolution of closed-loop strategies proposed for automating the different variables involved in the anesthetic process is presented herein.

Most of the studies published so far have focused on the control of hypnosis. Since the emergence of BIS in the mid-1990s, several researchers have considered this metric for quantifying the DoH. In 1998, Mortier et al. presented an algorithm capable of using the BIS as a feedback variable to adjust the target effect-site concentration for TCI systems [72]. This proposal studied the applicability of a patient-individualized adaptive model-based control of propofol by BIS incorporating TCI technology together with PK-PD model. The previous results were validated in the clinical field. The analysis showed clinically acceptable performance for the management of anesthesia [73]. In 2001, Sakai et al. proposed a PID solution based on BIS [74]. Promising results were reported when testing the algorithm on three patients undergoing general anesthesia. In 2002, Absalom et al. proposed a PID closed-loop strategy for the control of hypnosis based on BIS [75]. Like the previously published studies, the objective of the controller was to adjust the target effect-site concentration for a TCI system. The results showed the advantages of using a closed-loop scheme, although they revealed the need for robustness to cope with variabilities coming from external stimuli and patient variabilities during the intervention. In 2006, Liu et al. tested an empirical proportional-differential control algorithm to update the propofol infusion rate [76]. The performance of this algorithm was compared with the results achieved when performing manual dosage. The main conclusions revealed the ability to improve the induction and maintenance phases, together with a reduction in propofol consumption.

The advances observed when using closed-loop schemes to manage hypnosis, together with the need to solve emergent challenges, furthered the development of new control strategies for

hypnosis. Dumont et al. worked on a proposal for robust controllers to deal with the presence of patient variabilities involved in the process. Specifically, the objective was to develop a controller capable of providing an adequate drug administration regime for propofol, preventing under and over dosing, compensating the drug response variability, and rejecting disturbances to attain good set point responses [77]. These studies have focused on the synthesis and testing of robust PID controllers to deal with uncertainty in the clinical response of pediatric patients [78]–[80]. Unlike previous studies, the feedback information was based on the NeuroSense monitor. Some other strategies have been based on proposals for model-based predictive controllers [81], [82]. Although promising results have been reported in simulations, further research should be carried out in the clinical field to demonstrate the suitability of the strategy. Alternatively, recent approaches have opted to include artificial intelligence algorithms to improve the results presented so far [83]–[85]. However, the advantages and relevant improvements need further discussion.

Closed-loop for neuromuscular blockade has also been widely researched. The first proposals were described in the mid-80s [86], [87]. The early development of these strategies relied on the availability of clinical devices capable of quantifying the patient's muscle block during anesthesia. Closed-loop control has outperformed manually set infusion, achieving a steadier level in terms of neuromuscular blockade [88]. Although some solutions have been developed recently in this area [89], the improvement of the current state of the art is debatable, mainly for two reasons [90]: overdosing of neuromuscular blockade has little effect on patient recovery, and the effect can be reversed by other drugs, such that accurate and continuous actions are not required.

Unlike for the control of hypnosis and neuromuscular blockade, a limited number of contributions for automating analgesia have been presented. A lack of knowledge in the nociceptive process, together with the absence of a metric to monitor intraoperative analgesia, have conditioned the development of control strategies. The published works have focused on multiple-input single-output (MISO) and MIMO controllers capable of coping with the dosing of both hypnotic and analgesic drugs simultaneously. To this end, the DoH level has been considered to guide the drug delivery. The main hypothesis of these studies involves the idea that noxious stimuli has an influence on the DoH. A controller based on a cascade structure

with a dual proportional-integral-derivative algorithm was presented in [91]. A rule set was defined for titrating both propofol and remifentanil based on variations in the BIS signal. It was observed that this solution was clinically feasible and more precise than manual control to maintain the BIS within an appropriate range for anesthesia. Other studies have considered the introduction of the M-entropy monitor, as it has been observed to be more sensitive to noxious stimuli intensity changes [92]. The controller was based on a cascade structure with a proportional-integral-derivative algorithm associated with a target-controlled infusion device. Variations in the NeuroSense monitor have been also considered as a feedback variable for guiding remifentanil titration in [93]. This strategy presented an approach for extending a SISO DoH controller, using propofol and EEG-based monitoring, into a MISO controller by adding closed-loop remifentanil infusion. The resulting design yielded successful results in 80 clinical cases [94]. A recent study proposed extending this strategy to the direct habituating control framework by including two user-defined setpoints: a setpoint for the desired DoH, and a second setpoint for the baseline remifentanil infusion. This system was robustly stable and could provide safe anesthesia and analgesia for the patient population considered, improving disturbance detection [95]. A linguistic rule-based controller to incorporate the experience of the anesthesiologists was also presented in [96]. It consisted of three decision tables, two of which were used for remifentanil titration, while the third represented a SISO fuzzy PI controller for changing the propofol infusion rate. This controller considered variations in the DoH together with the surgical stimuli performed, although this proposal was only tested in simulation. Regardless of the controller presented in the previous proposals, the main limitation of any opioid control system was the absence of a specific measure to quantify the intraoperative analgesia level. Determining whether remifentanil administration was adequate with the presented closed-loop controller was thus challenging.

Conversely, different proposals based on specific monitors that claim a quantitative measure of the analgesic level have been presented. In [97], the Analgoscore variable was used to guide remifentanil administration in a closed-loop form. The amount of remifentanil infused was calculated with a fuzzy logic algorithm. During the vast majority of the operating time, excellent or good analgesia was achieved. The hemodynamic information has also been considered in closed-loop analgesia. In [98], an MPC controller was developed that considered two

independent SISO loops for both hypnosis and analgesia. This study assumed that propofol and remifentanil acted only on BIS and mean arterial pressure (MAP), respectively. The controller was only tested in simulation. Heart rate (HR), heart rate variability (HRV) and MAP were also considered in [99]. In this study, the experience of the anesthesiologists was translated into a set of fuzzy rules for remifentanil titration. This solution proved to be clinically acceptable, allowing for a clinically practical, nearly fully automated infusion of an opioid during medium-length surgical procedures with acceptable technical requirements and adequate precision.

Analogously, different schemes aimed at *total* control of the anesthetic process have been presented [100]. An automatic system for closed-loop administration of intravenous anesthesia drugs was presented in [101]. This study introduced McSleepy, an automated expert-based closed-loop delivery system that monitors all three components of general anesthesia and administers appropriate doses of the respective drugs, achieving fully automated control for inducing and maintaining anesthesia. The BIS was used as the control variable for hypnosis to calculate propofol infusion rates. The Analgoscore was used as the control variable to titrate the effective dose of remifentanil. Train-of-four (TOF) ratios were automatically computed and sent to the anesthesia delivery system for muscular blockade. This pharmacologic robot combined a proportional integral derivative-controller with a controlling feedback system using self-adaptive algorithms. The McSleepy closed-loop system showed better control of hypnosis and antinociception, shorter periods of over or undershoot of hypnosis, and faster extubation times than manually administered anesthesia. McSleepy was also tested for cardiac surgeries in [102]. The main novelty was the introduction of NociMap, a modified version of Analgoscore as the feedback variable to quantify the nociception level. The system demonstrated it was capable of maintaining adequate levels of both hypnosis and analgesia. The closed-loop system maintained anesthesia for procedures in 80% of cases without any human intervention, although further trials should be conducted to study the main limitations found.

Although significant progress has been made so far, the challenge remains to propose a system for the total control of the anesthetic process and its clinical validation. First, the field of automatic control of analgesia has been almost unexplored. The lack of a metric capable of quantifying the level of analgesia during surgery has slowed the development of controllers for this variable. Further studies should be conducted to ascertain the physiological process behind

analgesia. Specifically, a reliable and robust metric to quantify analgesia will be required to develop new strategies for the total control of anesthesia. In addition, the proposal of a model capable of dealing with drug interactions, as well as with patient variabilities, seems to be another unavoidable step before a comprehensive solution can be proposed. It is precisely the variability observed in patients' response that is emerging as one of the main limiting factors when proposing a closed-loop structure. Thus, a trade-off between robustness and individualized solutions must be analyzed. This will be especially relevant for controlling the DoH, where most of the proposals have been presented. This analysis must also include a study of the benefits introduced by the different algorithms previously presented, as well as the identification of those clinical and technical factors likely to limit the performance of the strategy.

1.5. Measurement of analgesia: where are we?

The state of the art of the principles for measuring analgesia during the anesthetic process is presented in this subsection. A review of the main monitors available is provided, and the results achieved in clinical practice are summarized. In general, the presence of autonomic reactions such as tachycardia, hypertension, sweating or lacrimation have been viewed as clinical signs to guide the analgesic process. Commonly, the clinical protocols to assess analgesia assume that nociception is evidenced by means of an increased blood pressure (BP) and heart rate. It means that adequate antinociception is related to stable circulatory parameters [103]. However, these variables can be affected by some other clinical process that turns these measurements into unspecific signs to evaluate nociception. Thus, a lack of sensitivity and specificity in these traditional measurements makes the development of new indexes a fundamental step for accurately managing analgesia [104]. As a matter of fact, different research has been conducted to both propose and test the suitability of new variables that claims a correlation with the nociception process. Recently, different devices based on these principles have been developed. The different mechanism for monitoring nociception-anti-nociception are presented in Figure 1.4. In this subsection, these mechanism are reviewed as per the structure proposed in [41], [42].

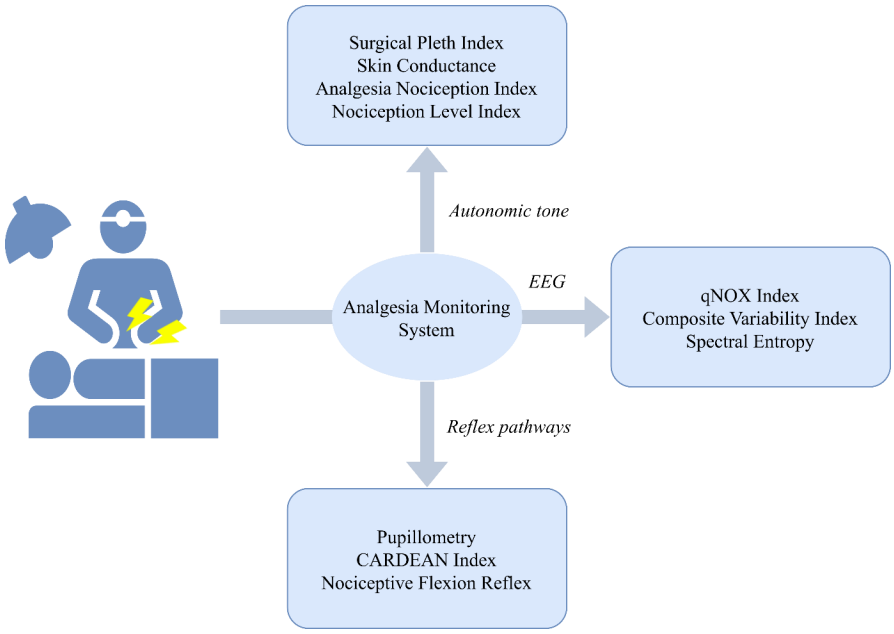

Figure 1.4. Diagram of the main mechanisms for monitoring nociception based on the source of the measurement. EEG: electroencephalogram.

1.5.1. Variables based on electroencephalography

Variables derived from EEG have been mainly used to assess unconsciousness during anesthesia. However, EEG variables may add information about the nociception balance [105]. The usefulness of EEG-based variables in detecting nociception balance is controversial. Further randomized clinical trials need to be evaluated to test the suitability of these monitors. The main EEG-based variables for measuring nociception are described below.

qNox index

qNox index, implemented in the qCON 2000 monitor (Quantium Medical, Mataró, Barcelona, Spain), is computed from the frontal EEG to monitor nociception. This index was developed using an empirical approach based on clinical data registered from 590 patients. Four frequency ratios from the EEG are recorded and compared with a reference scale obtained from

the database [106]. To assess the nociception level, an adaptive neuro fuzzy inference system (ANFIS) was proposed. This fuzzy system generates the output on a 0 (absence of nociception) to 99 (nociception) scale. In [107], it was found that qNox has a predictive value for response to noxious stimulation, such as laryngeal mask insertion; however, when using this index to predict acute pain in the PACU, no correlation was found [108]. Nowadays, there is insufficient evidence to draw any firm conclusion about the clinical use of this index [109].

Composite Variability Index

The initial development of the Composite Variability Index (CVI) algorithm was based on a retrospective dataset of 307 patients presented in [110]. It was found that the standard deviations of BIS (sBIS) and EMG (sEMG) were both significantly higher at the time of a somatic event compared to the values five minutes before. The results of this analysis identified a weighted combination of three variables, sBIS, sEMG, and BIS, which provided the best discrimination between somatic events and nonevents. The resulting CVI algorithm increased according to an increased incidence of somatic response during general anesthesia with propofol-remifentanil or sevoflurane-remifentanil. In [111], CVI was compared with changes in BIS, HR and MAP in relation to the level of antinociception and somatic response to a stimuli. Similar conclusions were found in [112] when measuring the increase in CVI after a noxious stimulus, in which low levels of analgesia with acceptable sensitivity and specificity were reported. However, although CVI showed a better correlation with somatic response to noxious stimuli, no relationship was found between CVI and opioid concentration in the absence of stimuli. In fact, unstimulated CVI depends more on the hypnotic drug effect than on opioid concentration [113].

Spectral Entropy

Spectral Entropy is based on two values of entropy, namely the state entropy (SE) and the response entropy (RE). SE is computed over the frequency range from 0.8 to 32 Hz, which includes the EEG-dominant part of the spectrum and reflects the cortical state. RE is computed over a frequency range from 0.8 to 47 Hz, including both the EEG-dominant and the electromyographic (EMG)-dominant part of the spectrum. The outcome is an index that ranges

from 0 to 100 to quantify the analgesic level. In [114], the effect of a skin incision performed 14 min after induction on different physiological variables was analyzed by means of a logistic regression. Although RE showed discriminative capabilities related to analgesia, SE did not. Similar conclusions have been reported in [115], where the presence of noxious stimulations affected the difference between SE and RE, although this difference was not always related to inadequate anesthesia. By contrast, no differences have been reported when analyzing sensitivity of RE and SE for guiding the use of opioids during general anesthesia [116]. Another limitation has been reported in [117], [118], as RE, based on muscular frequency analysis, did not allow analgesic evaluation in paralyzed patients.

1.5.2. Variables based on autonomic tone/response

The influence of the nociceptive process on the autonomic nervous system has emerged as an interesting approach to quantify the sympathetic-parasympathetic balance. To this end, the effect of analgesia on some clinical variables related to the autonomic response of the patient has been researched.

Surgical Pleth Index

The Surgical Pleth Index (SPI) is computed from a balanced sum of normalized heart beat intervals (HBIs) and plethysmographic pulse wave amplitude [119]. This proposal relies on the idea that both clinical variables are controlled by the sympathetic and parasympathetic tone balance, and thus SPI is capable of quantifying both the intensity of surgical stimulation and the depth of analgesia. Different research has been conducted to test the suitability of this measure as a feedback variable for analgesia management. However, some disputes can be found in the literature. In [120], the performances of SPI and hemodynamic variables were compared when a noxious stimulation was applied under general anesthesia. The authors concluded that combining information from SPI, MAP and HR offered the most accurate prediction. In [121], SPI reflected nociceptive stimulation during sevoflurane-remifentanil anesthesia when applying nociceptive events. Although this may indicate a quantification of the nociception-anti-nociception balance, further evaluations of SPI as a guidance variable for analgesia need to be performed. Some other studies, however, reached opposing conclusions.

In [122], the response of SPI under the effect of a fluid challenge may confound the interpretation of SPI as a surrogate measure of the nociception-anti-nociception balance. In addition, other investigations evidenced that SPI rose under noxious stimulation by intubation and incision, but it was not predictive of the hemodynamic responses [123].

Some other clinical studies have evaluated the SPI index as a feedback variable to guide the analgesic drug titration compared with traditional hemodynamic criteria. On the one hand, some studies claimed that adjusting the remifentanil dosage according to the SPI in outpatient anesthesia reduced the consumption of both remifentanil and propofol and resulted in faster recovery [124]. In addition, sensitivity and specificity of SPI to discriminate between low, moderate and severe pain levels was found to be moderate [125]. It was observed that both Numerical Rating Scale (NRS) and SPI correlated significantly with total opioid consumption. On the other hand, some other investigation concluded that higher doses of fentanyl were required intraoperatively with lesser postoperative rescue analgesic requirements when SPI was used to guide intraoperative analgesia as compared to conventional analgesia techniques [126]. Furthermore, Colombo et al. concluded that although SPI-guided analgesia evidenced a more stable sympathetic modulation, no differences in remifentanil consumption, recovery time from anesthesia, or postoperative pain and complications were observed [127].

One potential explanation for the inconclusive results presented so far may be the lack of evidence for selecting meaningful SPI target values. Different studies have been conducted to study the recommended thresholds for interpreting SPI. Specifically, SPI > 30 improved sensitivity and specificity to predict moderate-to-severe pain in the post-anesthesia care unit, although further studies should be conducted [128], [129]. In addition, SPI does not appear to be valid in children compared with the standard techniques [130], [131].

Skin Conductance

Pain has been related to increased subcortical and cortical activity, affecting the sympathetic tone and stimulating sweat gland secretion, leading to changes in skin conductance [132]. Regarding this physiological mechanism, different proposals have been presented to monitor analgesia in patients; however, unpromising results have been reached. Skin conductance (SC)

and the number of fluctuations in skin conductance (NFSC) have been considered for testing the suitability of this measure. NFSC was sensitive to clinical stress during surgical stimulation and could be used together with SC to differentiate stress situations [133]. A relationship between self-reported pain and NFSC has also been found in girls, but not in boys [134]. The same study did not find any correlation between NFSC and patient age. Despite that, most of the studies conducted so far have shown that skin conductance is not enough to quantify postoperative pain intensity [135], detect the effect of a painful stimulus compared to traditional variables [136]–[138] or predict insufficient analgesia during surgery [139].

Analgesia Nociception Index

The Analgesia Nociception Index (ANI) is a commercial solution developed by Mdoloris Medical Systems based on monitoring the nociception/antinociception balance. This index analyzes respiratory sinus arrythmia (RSA) as a measure of the parasympathetic component of the ANS. The ANI is a numerical value that varies between 0 and 100 to quantify the activity of the parasympathetic component [140]. The analysis of heart rate variability for ANI has been described elsewhere [141]. This monitor has been widely researched to test its suitability as a feedback variable to guide the analgesic process in anesthesia.

Several researches have been conducted to study the reactivity of the ANI monitor in response to noxious stimuli during anesthesia. In general, it has been observed that ANI is more sensitive than the hemodynamic variables [142], [143] or BIS [144], specifically at lower analgesic rates [138]. However, no evidence of the prediction of a possible inadequate nociception-antinociception balance has been found so far in these analyses [145]. ANI has been also compared with self-assessment of pain by means of NRS. Most of the published studies have found a significant negative linear relationship when evaluating immediate postoperative pain with values of ANI recorded throughout the surgery [146]–[150]. Other research has focused on evaluating intraoperative ANI-guided analgesic administration, with inconclusive results. Although many studies have shown a reduction in intra-operative opioid consumption, the impact on both postoperative pain and rescue analgesic consumption is debatable [151]–[153]. Other studies have proposed new variables derived from the ANI. Particularly, variations in ANI has provided better performance than static values in predicting

hemodynamic reactivity general anesthesia [121], [154], [155]. In addition, other published works have analyzed the cut-off values for detecting pain in conscious postoperative patients, resulting in divergences with those suggested by the manufacturer for use in the intraoperative state under general anesthesia [156], [157].

1.5.3. Variables based on reflex pathways

Pupillometry

Pupillary reflex dilatation was first proposed by Budge in 1852 as a sympathetic spinal reflex that dilated the pupil after noxious stimulation [158]. This mechanism has also been considered for the postoperative evaluation of analgesia, especially in uncommunicative patients [159]. In anesthetized patients, experimental noxious stimulus increases both pupillary diameter (PD) and pupillary light reflex amplitude (PLRA) [160], [161]. For an accurate measurement, pupillometers based on infrared and video technology have been developed. The first experiments focused on validating pupillometry as a reliable index of pain intensity for opioid titration in the postoperative period. It was noted that the pupillometry measurement was significantly correlated with the NRS [162]. Pupillometry also improved the ability to assess the pain of patients compared with ANI [163]. These experiments concluded that pupillometry could be used to guide morphine administration in the immediate postoperative period. This technique has also been evaluated for predicting pain intensity during the surgical procedure [164]. It was observed that the pupillometry may potentially guide caregivers to adjust analgesia before noxious procedures. Different studies to evaluate pupillometry as a monitor of intraoperative analgesia have been also conducted. In [14], patients were divided into two groups in which the remifentanil dosage was guided by either pupillometry or hemodynamic variables. In the postoperative period, visual analogue scale (VAS) was used to assess pain. Monitoring of the intraoperative analgesia by pupillometry was able to reduce the intensity of acute postoperative pain and analgesic consumption in the first 12 h after major gynecological surgery. Similar conclusions were reached in [165], [166]. Successful results were also found when using pupillometry to evaluate the response to nociceptive stimuli under propofol and ketamine anesthesia in [167], [168]. The pupillary pain index (PPI) was first evaluated to determine the variations in the index when a bolus of alfentanil was supplied in [169]. There

was a significant decrease in PPI after alfentanil administration. The results of this pilot study suggest that the PPI score decreases when the level of analgesia increases. In general, the main limitation of pupillometry comes from the inconvenience of taking several measures throughout the surgery, which involves opening the eyes of the patients continuously. As a consequence, effects on the depth of hypnosis have been reported [169].

CARDEAN Index

The cardiovascular depth of anesthesia index (CARDEAN) was developed to predict unexpected intraoperative movements in anesthetized unparalyzed patients. During a noxious stimulus, the autonomic response increased blood pressure, followed by an increase in heart rate. This phenomenon was translated into a 0 to 100 index to monitor analgesia. This index is based on the beat-by-beat R-R interval and systolic blood pressure time-series analysis. CARDEAN was written retrospectively as presented in [170]. CARDEAN > 60 predicted movement in 30% 15s to 274s before the movement. This index was tested prospectively for validation in [171], where the capability of the index to reduce the incidence of unexpected movements, and thus reflecting intraoperative nociception, was evidenced. Similar results have been presented in [172]–[174]. However, the capability of this index to guide the administration of opioid analgesics has not been studied so far. Further studies must be carried out to test the suitability of CARDEAN to monitor analgesia.

Nociceptive Flexion Reflex

The nociceptive flexion reflex (NFR), also known as R-III reflex, is a physiological reflex allowing for painful stimuli to activate an appropriate withdrawal response [175]. R-III is based on the measurement of spinal reflexes induced by stimulus in all four limbs. However, the electromyographic activity of the biceps femoris muscle is preferred for monitoring analgesia [176]. An NFR threshold can be defined by applying electrical stimuli to the sural nerve as described in [177]. Based on the EMG response, the intensity required to elicit the R-III reflex can be used to define an objective measure of the individual nociceptive threshold [178]. Although some successful results showing the ability of R-III to predict movement responses

to noxious stimulus have been presented [179]–[182], further research must be conducted to test the validity of this measurement to guide opioid administration during anesthesia.

1.5.4. Multi-parameter score

The Nociception Level index

The nociception level index (NOL) was first presented in [183] as a combination of multiple physiological parameters capable of quantifying the nociception level. This combined index includes information on heart rate, plethysmograph wave amplitude, and skin conductance. Both linear and nonlinear NOL indexes were proposed to incorporate the clinical parameters into a single index. Different studies have been conducted to test the suitability of the index as a reliable metric for monitoring analgesia. The capability of NOL to monitor noxious stimulation compared with traditional variables has resulted in promising results, as reported in [184]–[186]. In addition, variations in this index under different analgesic drug doses have also shown that NOL is capable of monitoring nociception intensity during general anesthesia [187], [188].

NOL has been used to guide sufentanil administration in [189]. This study concluded that doses of opioids mainly depend on the monitoring device used. Thus, further studies must be performed to analyze the clinical applicability of NOL for guiding opioid administration.

1.5.5. Limitations of current proposals

The analysis presented indicates that the techniques used so far to validate the proposed mechanism for monitoring analgesia have some limitations. First, some of the published studies have proposed a self-evaluation of postoperative pain in PACU and its correlation with the information provided by the new monitors. To this end, some metrics like VAS or NRS have been used. However, the patient's conscious assessment fails with communication impairments and cannot distinguish psychogenic from somatic pain [190]. Thus, the self-evaluation may be affected by subjectivity. Some other studies evaluate the capability of the monitors to assess the intensity of noxious stimuli for different effect concentrations. To this end, invasive painful stimuli apart from those purely derived from the surgery are applied. This may compromise the

safety of the individuals undergoing these studies, causing stress episodes during the surgery. Other published studies rely on using these monitors as feedback variables to guide drug administration. In general, these studies assume that drug consumption is a measure to quantify the performance of the analgesic process. However, there is no evidence to correlate the consumption of analgesics with the quality of the analgesic process. In conclusion, despite the large number of studies presented, none of them have offered decisive results that can be considered of current clinical relevance. Further analysis based on new methodologies to test the suitability of a monitor to guide the drug titration, including a greater number of patients and types of surgeries, must be performed

1.6. Outline

This doctoral thesis is presented as a compendium of publications. It includes three original research papers which have been published in different scientific journals. Additionally, a paper which is currently under review for publication has been also included due to its novel findings. In keeping with the requirements provided by the regulations for official doctoral studies at the Universidad de La Laguna, this document is structured as follows.

After this introductory chapter, which justifies the thematic unity of this work, the main objectives of the thesis are presented in Chapter 2. A summary of the main methodologies used in the different articles is included in Chapter 3. Each subsection briefly describes the methods used in each paper. The main results of the research, as well as the discussion, are presented in Chapter 4. The results of the different articles have been grouped according to the main objectives of this work. Chapter 5 provides the general conclusions drawn from this thesis and proposes future research directions.

The original publications included in the compendium are presented in Appendix A. Appendix A-I proposes a novel scheme to evaluate the suitability of including a new variable in a clinical decision-making process. This paper describes a whole procedure, from the data acquisition to evaluating the results based on a fuzzy inference system. Finally, this algorithm is contextualized to the analgesia assessment scenario, where the Analgesia Nociception Index monitor is studied. Appendix A-II further studies the capability of the ANI monitor to provide

valuable information aimed at replicating the anesthesiologist's decisions during surgery. To this end, artificial intelligence-based techniques are proposed to analyze the advantages of the ANI monitor compared with conventional non-specific variables. Appendix A-III proposes an adaptive PK-PD model to describe the effects of propofol-remifentanil interactions on the depth of hypnosis during general anesthesia. Additionally, this solution deals with the presence of uncertainty due to the interpatient and intrapatient variabilities.

Appendix B includes a research work that is currently under review for publication in a scientific journal. Although it has not been published yet, this research shines a light on the closed-loop control of anesthesia. Specifically, this research proposes synthesizing a robust optimal filtered PID to deal with the uncertainty in controlling the depth of hypnosis. Also provided is an analysis of the main limitations introduced by this PID-based solution vs. a higher-order controller under the same technical and clinical considerations.

Finally, the works published by the author are listed in Research Items.

2. Objectives

The main objective of this work is to propose new solutions to address some of the current challenges involved in the total automation of the anesthetic process. Specifically, three main aspects will be addressed: i) the *assessment* of intraoperative analgesia by analyzing the Analgesia Nociception Index, ii) the proposal of a *model* to study the effects of the interaction between hypnotic and analgesic drugs on the DoH, as well as the pharmacological variabilities observed in the patient's response, and iii) the proposal of a robust optimal filtered PID controller and the main limitations introduced when comparing it with a higher-order algorithm to *control* the DoH.

First, the potential of a specific metric for monitoring the depth of analgesia to guide drug delivery during the anesthetic process is studied. Considering the current state of the art as well as the main conclusions presented in the literature, this work proposes an evaluation of the Analgesia Nociception Index. A novel methodology to ascertain the ability of the ANI to guide the decision-making process must first be proposed. Previous research has focused on a clinical validation to test the accuracy of this index when assessing the depth of analgesia under different conditions. This study aims to propose a new approach. Unlike previous research, this work addresses the suitability of the monitor to provide new useful information that could be included in the decision-making process for analgesic drug titration. This new perspective would make it possible to interpret and correlate the information displayed by the ANI monitor with the decisions made by the anesthesiologist as a first step toward the proposal of a closed-loop scheme for analgesia.

Taking recent research into account, the proposal for a MIMO structure aimed at the total automation of the anesthetic process will be based on individual closed-loop strategies developed to control hypnosis, analgesia and neuromuscular blockade. As a preliminary step, therefore, it will be necessary to address certain questions. On the one hand, the integration of individual controllers in a MIMO structure will have consequences for the controllers presented so far. This concern mainly arises from the pharmacological interactions between the hypnotic and analgesic drugs on the DoH, not included in most of the previous research published to date. Consequently, a new mathematical model capable of dealing with drug interactions required for the future development of a MIMO structure is proposed. On the other hand, it will

be necessary to determine which type of control algorithm and clinical factors should be considered to control each clinical variable involved in anesthesia. Regarding the state of the art, and given the importance of dealing with the uncertainty in the patient's response, this thesis focuses on synthesizing a robust optimal filtered PID controller for the DoH. In addition, the absence of a meaningful comparison to analyze the performance limitations when using PID structures against more recent complex proposals requires a systematic comparison considering the same clinical and technical requirements.

Consequently, the specific objectives proposed in this work are to:

1. Study the state of the art in closed-loop control in anesthesia. Specifically, main solutions proposed, considering the three main variables involved in the anesthetic process as well as current challenges, must be analyzed.
2. Study the state of the art in analgesia assessment. This study must include not only the traditional protocols currently used in clinical practice, but also recent research based on the introduction of new monitors.
3. Propose a new methodology to assess the suitability of including a new clinical variable in the decision-making process. On the one hand, this method must allow a preliminary study on the reliability of a certain clinical variable to guide the decision-making process. On the other hand, this scheme must be capable of translating into a set of rules the intrinsic relationship between the information displayed by a new clinical measure and the decisions made by an expert. To this end, a system based on a fuzzy algorithm synthesized from real data will be proposed.
4. Propose a new point of view to evaluate the Analgesia Nociception Index as a reliable feedback variable to guide the drug delivery process during anesthesia. This new perspective will be based on the adaptation of the methodology previously presented to the analgesia scenario. As a result, a clinical scheme, together with a new procedure for data acquisition and preprocessing, must be defined. This would constitute a first step toward analyzing the ANI monitor as a valuable feedback tool to consider during analgesic drug delivery.

5. Evaluate the Analgesia Nociception Index for assessing general anesthesia. This new approach will make it possible to study whether the decisions of the experts throughout the surgery can be replicated by considering the ANI monitor under different conditions. Specifically, the feasibility of using the ANI in the decision-making process to outperform the assessment of opioids traditionally based on non-specific hemodynamic variables will be analyzed.
6. Propose the basis for the development of future schemes that could rely on the ANI as a feedback variable to, first, define decision-support systems and, subsequently, synthesize a closed-loop controller for analgesia
7. Develop an adaptive model to represent the depth of hypnosis by taking into account the pharmacological interactions between hypnotic and analgesic drugs. This structure will be based on a parametric pharmacokinetic-pharmacodynamic model that can deal with uncertainties, such as patient variabilities as well as the variable time delays introduced by the BIS monitor.
8. Propose a robust optimal filtered PID controller to regulate the DoH. The synthesis of this controller will take into account the main relevant clinical factors that may have an impact on its performance, such as interpatient variability, the effect of surgical disturbances on the DoH and the noise introduced by the DoH monitor.
9. Compare the PID controller proposed with a higher-order LTI controller represented by the Youla parameters. This comparison aims to quantify main limitation introduced when using PID vs. a higher-order controller for DoH regulation.

It is important to note that the study proposed here is contextualized to clinical practice. The aim is to extract realistic conclusions and propose new and useful methodologies that are compatible with the conditions of standard surgical procedures in the operating room. This way, the results could be easily applied to clinical practice. In light of the above, this work seeks to enhance the state of the art in such a way that it could serve as a starting point for new research aimed at the total automation of the anesthetic process.

3. Methodology

This chapter summarizes the methodology used in this work to achieve the proposed objectives. Each subsection presents the methodology used in each article. A more detailed explanation of the methodology can be found in the articles included in Appendix A and Appendix B.

3.1. Synthesis of a novel fuzzy algorithm to introduce new variables in the drug supply decision-making process in medicine

The goal of this proposal is, first, to define a fuzzy logic-based general method to analyze the applicability of a new variable to be included in a decision-making process. Then, the methodology presented was contextualized to the evaluation of the Analgesia Nociception Index in the decision-making process during analgesia.

3.1.1. Proposal of a general fuzzy-based algorithm to introduce new variables in a decision-making process

This proposal defines a general procedure to assess whether a new variable provides new and valuable information to be included in a decision-making process. Unlike previous research in this field, instead of clinically validating the variable, this work proposes (i) a fuzzy-based algorithm to define a new standard to analyze the relationship between the information displayed by a new clinical variable and the decisions made by the experts based on a standard protocol, and (ii) a fuzzy inference system (FIS) capable of formalizing the relationship found in a set of rules.

Fuzzy systems have been widely used in medicine due to their simplicity in correlating linguistic rules with clinical concepts [190]. The use of fuzzy values allows clinicians to deal with uncertainty during the decision-making. Furthermore, fuzzy logic allows relating heuristic knowledge with a set of rules without using complex mathematical theory. However, the definition of the membership functions and the rule base is a difficult task if there is no heuristic knowledge behind the process. This turns analyzing the suitability of a new variable to be included in a decision-making process into a real problem. This study proposes fuzzifying a

decision tree in order to build a FIS automatically. To evaluate the results, different performance metrics were included. The methodology used is briefly described below.

Decision Tree

A decision tree (DT) is a supervised machine learning algorithm capable of making predictions to classify an observation from a finite set of classes. A general description of this algorithm can be found in [191]. A Classification and Regression Tree (CART) algorithm has been used to train the classifier from the dataset [192]. This algorithm aims to minimize the relative sum of squared errors in the two partitions resulting from a split. The Gini index was used as the splitting rule for the classification in this study [193].

Fuzzy Inference System

A fuzzy inference system is a fuzzy-logic-based structure capable of making decisions based on a set of *if-then* rules that maps fuzzy inputs and outputs [194]. Linguistic variables are described through linguistic values expressed as membership functions (MFs) that belong to a universe of discourse. A singleton fuzzification method was used for the fuzzification of crisp inputs. A Takagi-Sugeno inference system based on a constant output was proposed. Finally, a weighted average was used for the defuzzification method.

Fuzzification of the decision tree

A proper definition of the membership functions and the rule base to tune a FIS accurately mainly relies on the heuristic knowledge behind the process. Thus, the lack of knowledge of a system can turn the synthesis of a fuzzy system into a challenge. As a result, a data-based driven methodology was proposed to define the FIS. First, a decision tree must be trained to obtain a classifier from the real data. Second, the DT is fuzzified. The conditions in the test nodes set the limits of the membership function. The rules of the FIS are obtained from an evaluation of the DT by starting at the root node to the leaves, considering all possible combinations. Triangular and trapezoidal MFs are considered for intermedia and edge partitions of the universe of discourse, respectively. The limits of each MF are increased to achieve overlap

between the different categories. Finally, the numerical output values must be defined so that they can be correlated with the decisions that the expert handles.

Evaluation of the fuzzy decision-maker

To evaluate the capability of the resulting FIS to correlate the new decision variables proposed (inputs) with the decisions made by the experts (outputs), different performance metrics were computed. These measures included accuracy, precision, recall, sensitivity, specificity and the analysis of the receiver-operating characteristic (ROC) curve and the area under the ROC curve (AUC) [195]. To avoid overfitting during the training process, a cross-validation technique was applied [196].

3.1.2. Application of the novel fuzzy algorithm to the analgesia assessment scenario

Based on the general algorithm presented in 3.1.1, a study for the evaluation of the ANI monitor in the decision-making process during analgesia was specifically designed. To contextualize the general scheme to the analgesia assessment scenario, a conceptual scheme to deal with the main clinical and technical features of the problem was presented. The proposal defined the data collection for the training process, the preprocessing and analysis of the data, the design of the fuzzy inference system and the validation of the results.

State of the art in analgesia assessment

Before a scheme to adapt the general algorithm presented to the specific problem in analgesia was defined, the state of the art - including the current trend in clinical practice, analgesia monitoring and the study of the ANI - was examined.

The standard clinical practice to guide analgesic drug delivery during general anesthesia was first studied. Clinical documentation, as well as the expertise of the anesthesiology group at the Hospital Universitario de Canarias (HUC), was taken into account. The main standards for basic anesthetic monitoring developed by the Committee on Standards and Practice Parameters (CSPP) state that anesthesiologists monitor vital signs at 5-min intervals during the

perioperative period [197]. Specifically, the ASA standards explain that every patient receiving anesthesia shall have arterial blood pressure and heart rate determined and evaluated at least every five minutes. Therefore, in the absence of critical episodes, the anesthesiologist regulates the analgesic infusion rate every five minutes based on the hemodynamic changes registered. The anesthesiologist may also vary the infusion rate in anticipation of a surgical stimulus or in response to a clinical sign derived from inadequate analgesia, such as movements, sweating or lacrimation [41]. Regardless of the reason for the change, these decisions result in three possible actions: increasing, decreasing, or maintaining the infusion rate. In general, unless a drastic hemodynamic variation is observed, these changes are commonly applied in steps of constant magnitude for both increases and decreases.

In addition, a documentary analysis was conducted to ascertain the state of the art in analgesia monitoring. This analysis focused on the different techniques and devices clinically implemented for monitoring analgesia, as well as the different protocols specified to validate them. A comparative analysis of the different proposals was carried out. The main results, limitations, and conditions of the different studies were analyzed. Finally, a detailed study of the working principle of the Analgesia Nociception Index monitor was performed. The technical information was obtained through the technical sheets provided by the manufacturer, as well as from the different scientific articles published by the developers. In addition, several studies using the ANI monitor for its clinical validation were analyzed.

Development of the conceptual scheme

Considering the state of the art, a new scheme for both data recording and analysis to evaluate the ANI as a variable capable of providing useful information to guide the delivery of analgesic was devised. The scheme seeks to address the main weaknesses identified in the previously published studies:

- The validation of the ANI should not be based on the postoperative evaluation of the patient.

- The application of extra noxious stimuli during surgery must be avoided unless required for the clinical process. The analysis should rely on the real decisions made by anesthesiologists in a realistic scenario.
- A change in the analgesic drug infusion rate should depend solely on the criterion of the experts as a consequence of the clinical state of the patient. Other criteria that may influence the results must be avoided.
- For fairness of comparison, the decisions made by the anesthesiologist must rely solely on standard clinical protocols. Information displayed by the ANI monitor must not be available so as to avoid biasing the decision-making process.

Clinical protocol and data acquisition

A clinical protocol was specifically designed for this study by three anesthesiologists at the Hospital Universitario de Canarias. It was approved by the Ethics Committee for Clinical Research of the HUC. The protocol involved Total Intravenous Anesthesia (TIVA) with propofol for hypnosis and remifentanil for analgesia during cholecystectomy surgeries. A Bispectral Index monitor was used as a guidance variable for propofol titration. The dose of remifentanil was adjusted by the clinician based on the hemodynamic response, defined as a variation of more than 20% in heart rate and/or blood pressure for 5 min. Additionally, the anesthesiologist could change the remifentanil dose to prevent the effects of surgical stimuli during the process. Changes in remifentanil of up to 0.05–0.1 μg/kg/min were allowed.

For the data acquisition, information about heart rate, blood pressure, BIS, ANI and both remifentanil and propofol infusion rates were recorded during the surgeries. A PC ran a real time application developed in Matlab for the data acquisition. Information from the ANI and BIS monitors, as well as propofol infusion rates, were recorded automatically at a sample time of 5 s in the PC via a USB port. Two anesthesiologists took part in each intervention. Anesthesiologist 1 was in charge of the drug supply task. Anesthesiologist 2 oversaw the acquisition process and registered the variations in HR, BP and remifentanil changes in the Matlab application every 5 min. Crucial to this study is the fact that the information displayed by the ANI monitor was not available to anesthesiologist 1 to avoid biasing their decisions.

Thus, the data displayed by the ANI was recorded in parallel to the traditional drug supply process.

Data preprocessing

The data preprocessing involved all those tasks related to the verification, validation and correction of the data recorded during the surgeries. In general, the data preprocessing carried out included:

- Identification of the target information to be analyzed based on the main purpose of the analysis.
- Validation of the data recorded during the acquisition process.
- Formatting the data as per the analysis requirements.

Proposal of the decision variables

The criterion to interpret the ANI index during general anesthesia is debatable. Different proposals, including the optimal ranges of ANI for assessing analgesia as well as new ANI-derived variables, have been published. As a matter of fact, this study considered different variables to be correlated with the decisions made by the anesthesiologists. These decision variables included not only the raw values along different time intervals, but also the proposal of new ANI-derived variables to add the dynamic features of this index. In this study, two constant outputs were proposed: “decreasing drug”: 0 and “increasing drug”: 100. As a result, the defuzzification process resulted in an output ranging from 0 (decrease the drug) to 100 (increase the drug), with a threshold value of 50 to classify the two decisions.

Synthesis of a fuzzy inference system for the analgesia assessment application

Taking into account the specific characteristics of the problem for the analgesic drug supply, the methodology presented in section 3.1.1 was applied. The general scheme is depicted in Figure 3.1. Different fuzzy inference systems were synthesized to evaluate the relationship between the decisions made by the expert and the information displayed by the ANI monitor during the anesthetic process.

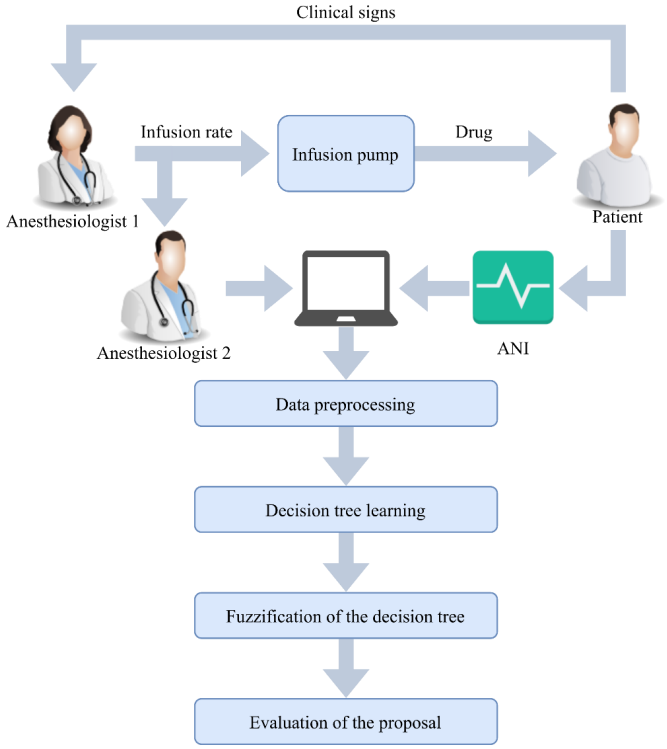

Figure 3.1. Scheme of the novel fuzzy algorithm adapted to the analgesia assessment scenario.

3.2. A machine-learning-based method for evaluating the Analgesia Nociception Index during general anesthesia

Considering the results obtained in the first study, and in order to continue with an in-depth evaluation of the ANI monitor as a feedback variable to replicate the expert's decisions, a second study was conducted. Specifically, this second study aimed to analyze the capability of using the ANI monitor to outperform the assessment of opioids traditionally guided by non-specific signs such as heart rate and arterial pressure. To this end, different machine learning classifiers were trained with several sets of clinical features. First, the classifiers were trained to predict only "increasing drug" and "decreasing drug" decisions. Then, the performance of the resulting proposal was evaluated under different scenarios observed in the clinical practice,

including those situations in which the remifentanil dose was kept. A summary of the methods is presented herein.

Machine learning algorithms

Different machine learning algorithms were included for the analysis. First, automated training was performed with the different algorithms to search for the best classification model types that resulted in the best performance. All the methods, as well as the parameters tested, were presented in [198]. According to the results of this preliminary analysis, four algorithms were finally included for a more exhaustive study:

- K-Nearest Neighbors (KNN). Number of neighbors was set to 1 and the Euclidean distance was used [199].
- Decision Tree (DT). Up to 4 splits were allowed and the Gini Index was used for the split criterion [200].
- Linear Discriminant Analysis (LDA). A linear discriminator with a gamma parameter set to 0 was proposed [201].
- Support Vector Machine (SVM). A lineal kernel function with a box constraint set to 1 and a kernel scale automatically selected was included [202].

Feature proposal

The feature proposal was key to the analysis, as it constituted the basis for the comparison. Unlike the input features proposed in 3.1, the input variables considered here also included information about the evolution of the parameters considered in standard clinical practice, i.e. heart rate and blood pressure. It was thus possible to compare whether introducing the information displayed by the ANI monitor was helpful to outperform the decisions based purely on the hemodynamic information. Specifically, four feature vectors were included for the comparison:

1. Hemodynamic information: This feature vector aimed to represent the standard clinical practice, as only hemodynamic information was included for training.

2. Minimum values of the ANI. This proposal included not only the hemodynamic information, but also some ANI-derived variables that focused on minimum ANI values recorded during the last 10 minutes before changing the drug dose.
3. Maximum values of the ANI. This feature vector included the hemodynamic information as well as some ANI-derived variables that focused on maximum ANI values recorded during the last 10 minutes before changing the drug dose.
4. ANI information: This vector only included information derived from the ANI index.

Evaluation of the proposal

The proposal was evaluated based on the analysis of how well the different machine learning algorithms were able to match the decisions made by the expert in the clinical practice. Specifically, the proposed comparison was divided into three steps. First, the suitability of the four machine learning algorithms to predict the decisions made by the experts was studied. Second, the comparison focused on the performance achieved by the best-performance machine learning algorithm depending on the different input feature vectors proposed. Different performance indicators were computed to this end: accuracy, specificity, precision, recall, AUC and Kappa index [203]. To deal with possible overfitting problems, a 3-fold cross validation was repeated 100 times to study the prediction capability of each model while minimizing the high variability expected in the results due to the fold configuration. Thus, both mean values and variations resulting from the 100 iterations were eventually analyzed. Finally, the best classifier was tested under three scenarios representing the real situations observed during general anesthesia. These scenarios comprised an urgent change of dose, a non-urgent change of dose and keeping the current dose. Since the trained classifier was dichotomous, the analysis of the posterior probability associated with each prediction was included in the evaluation [204].

3.3. Proposing an adaptive drug interaction model to predict the depth of hypnosis during anesthesia

To obtain an accurate PK-PD model capable of representing how the hypnotic and analgesic drugs interact with the DoH, an identification algorithm based on optimization techniques was developed. The Bispectral index was proposed to measure the depth of hypnosis, as it is one of

the preferred options among clinicians [205]. The structure presented was based on a parametric pharmacokinetic-pharmacodynamic model capable of dealing with (i) interpatient and intrapatient variability through an iterative identification algorithm to adapt the model parameters, (ii) propofol-remifentanil interactions, considering the additive effect of both drugs, and (iii) variable time delays introduced by the BIS monitor. The algorithm was validated with clinical data. A brief model description is presented herein.

Model description

The proposed model structure was based on a PK-PD representation to describe the effect of the drugs in the body. The PK model, here based on a three compartmental and an effect site compartment structure [206], was represented through mathematical differential equations to model the dynamic distribution of propofol and remifentanil drugs through the different compartments. The PD model to relate the effect concentration with the BIS index was represented through a nonlinear sigmoid function, also known as an Emax model [207]. Schnider and Minto models were considered for modeling propofol and remifentanil, respectively [208], [209]. To model the additive interactions between propofol and remifentanil observed in the clinical practice, Bouillon's proposal based on a nonlinear model presented in [210] was considered.

To take into account the variations in the BIS response between the different patients (interpatient variability) as well as the variations observed in the same patient throughout different stages of the surgery (intrapatient variability), an iterative identification algorithm to update the parameters of the PK-PD model was proposed. An additional goal was to identify the variable time delay introduced by the BIS monitor. This source of delay is due to the variable processing time to attenuate the presence of artifacts during surgery.

Optimization-based identification algorithm

The main objective of the algorithm proposed was to identify the parameters involved in the PK-PD model to characterize the individual response of the patient. A nonlinear least-square solver was used to minimize the error between the real evolution of the BIS during the clinical

practice and the prediction of the model while identifying the parameters. The algorithm was divided into two parts:

1. Induction phase. First, the model is identified from the data recorded as anesthesia is induced. This is a preliminary identification to initialize the algorithm for the maintenance phase.
2. Maintenance phase. The model previously identified is kept until the online comparison between the predicted BIS and the real BIS differs by > 10% for 5 minutes, at which time the identification algorithm is run again considering the most recent information from the clinical data. The updated model is kept for the next 5 min (at least). Then, the prediction error is recomputed.

Evaluation of the proposal

To evaluate the strategy presented, the prediction mean square error (PMSE), the median performance error (MDPE), and the median absolute performance error (MDAPE) were calculated [211]. To assess the suitability of including an adaptive model for BIS prediction, the results were compared with those obtained by a non-adaptive model only identified once at the beginning of the maintenance phase by means of the same optimization algorithm.

3.4. Design and analysis of a robust optimal filtered PID in propofol anesthesia

The methodology to synthesize a robust optimal filtered PID for propofol anesthesia is presented herein. The main objective was to minimize the effect of the surgical stimuli on the DoH while meeting both clinical and technical requirements. In addition, the main limitations introduced when comparing the resulting PID vs. a higher-order LTI controller for propofol anesthesia were also analyzed.

3.4.1. Synthesis of a robust optimal filtered PID for propofol anesthesia

The block diagram illustrating the closed-loop system is shown in Figure 3.2. A set of clinical considerations were taken into account for the design of the controller to ensure an admissible range of the DoH during the surgery. First, the controller needed to attenuate the effect of surgical disturbances in order to reduce patient awareness while minimizing the risk of hemodynamic responses. The closed-loop system also needed to be insensitive to high frequency measurement noise, typically associated with the DoH monitor. Last but not least, the interpatient variability observed in the response to therapy emerges as one of the main limiting factors to be considered in the design. Thus, the resulting controller had to be robust to the uncertainty introduced.

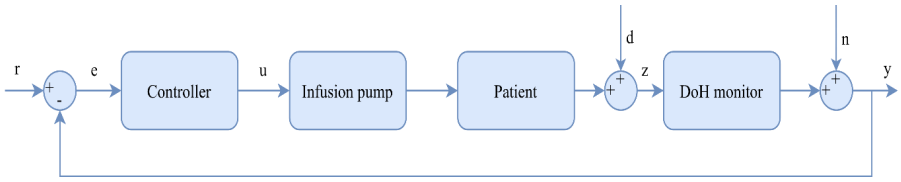

Figure 3.2. Block diagram of the closed-loop system. r: DoH setpoint; u: propofol infusion rate; z: DoH; y: measured DoH; d: surgical disturbance; n: measurement noise.

Modeling the anesthetic process

A model-based synthesis of the controller was proposed in this study. To represent the variability in the response of the patients, a set of 47 validated pediatrics PK-PD models presented in [49] was considered. A more conservative characterization of the variability set in the model was also provided by an unstructured additive uncertain model. Instead of using the BIS monitor to measure the DoH, the use of the NeuroSense WAV_{CNS} monitor was assumed [212]. It is similar to the BIS but comes with the advantage of time-invariant response dynamics, making it more suitable for closed-loop applications. No explicit actuator model was employed as modern remote-controlled infusion pumps are essentially static and linear, with negligible quantization effects. To model the exogenous disturbances, a step added to the patient output was considered to represent the surgical stimuli. The measurement noise was added as a white noise model to the DoH monitor output.

Optimization based controller design

The control objective was to attenuate the surgical disturbance from the DoH. The L_2 norm of the monitored DoH resulting from a disturbance step was minimized. To ensure the robustness of the design, H_∞ constraints on the sensitivity function, S, and its complement, $T = 1 - S$, were imposed. Measurement noise was attenuated by imposing an H_2 constraint on the transfer function from noise to the control signal. Response undershoot was limited to 10 WAV_{CNS} preventing the worst case undershoot associated with the 50 WAV_{CNS} to bring the DoH outside the recommended 40 – 60 WAV_{CNS} interval for general anesthesia.

The parameters of the PID controller and filter were co-optimized considering these constraints. The parametrization presented resulted in a non-convex synthesis problem approached with a two-stage method. First, a global optimization was performed. Second, to verify local optimality, a gradient-based optimization was run. Finally, to study the effect of the interpatient variability in the performance, three different designs were proposed:

1. A PID controller based on the model set.
2. A PID controller based on the additive uncertain model.
3. Individual PID controllers based on each model in the set.

3.4.2. Comparison of the robust optimal filtered PID controller vs. a higher order LTI controller

The main objective of this comparison was to analyze the performance limitations associated with using the filtered PID controller previously synthesized, as compared to a high-order controller. This study proposed synthesizing the Youla parameter to provide an upper bound on performance increase when moving from a filtered PID to an LTI controller of arbitrary order.

Youla synthesis

The Youla parametrization, Q, characterizes all stabilizing controllers for a linear plant. Based on this premise, and considering a suitable representation of a general controller transfer function, convex optimization was applied to search for the optimal controllers when evaluating

the 47 individual models in the set. The same objective and constraints on sensitivity, complementary sensitivity, control signal response to measurement noise, and minimum undershoot were assumed for fairness of comparison. The Ritz approximation was used to express *Q*. All the constraints considered were closed-loop convex, such that a solution was found efficiently. All the solutions were checked for constraint violations.

Evaluation of the proposals

A two-step comparison for the evaluation of the designs was performed. First, the benefit of increasing the controller order when comparing the individual PID controllers with the Youla parameters was studied. Second, the performance limitation imposed by the interpatient variability was evaluated by comparing the individualized PID controllers with those optimized to be robust over the model set and the uncertain model. The optimization cost was analyzed accordingly. All the solutions were checked for constraints violations. Finally, to further investigate the clinical feasibility, the resulting controllers were evaluated in a simulation using the 47 nonlinear patient models.

4. Results and discussion

The main findings of this work as well as the discussion of the results are presented in this chapter. The results published in the different articles have been here grouped according to the three main objectives aimed at this thesis.

4.1. *Assessment* of intraoperative analgesia by analyzing the Analgesia Nociception Index

A novel fuzzy algorithm to introduce new variables in the drug supply decision-making process in medicine

This work proposed the basis of a new scheme to analyze the benefits of introducing a new clinical variable in a decision-making process. While previous studies have mainly focused on the clinical validation of new monitors, this approach evaluated the suitability of a new variable to provide valuable information aimed at replicating the decisions made by an expert in clinical practice. This proposal formalized the whole procedure, from the data collection and preprocessing, to the synthesis of a fuzzy inference system based on a decision tree for the analysis.

Specifically, this novel fuzzy algorithm was contextualized to the study of the ANI monitor. The state of the art on analgesia monitoring showed that the Analgesia Nociception Index provides a promising tool in clinical practice. This monitor is based on a noninvasive system that displays a continuous index related to the Autonomic Nervous System (ANS) through heart rate variability. The ANI monitor displays two variables ranging from 0 to 100: instant ANI (ANI_i) and mean ANI (ANI_m). While ANI_i is directly related to the reactions of the patient to painful stimuli, ANI_m is related to the effects of analgesia on a patient. For unconscious patients under general anesthesia, keeping ANI_m in the 50–70 range has been recommended to avoid unwanted hemodynamic events [144]. Nowadays, however, no clinically relevant results have been achieved to prove the suitability of this monitor in analgesia assessment. This work came up with a scheme based on a noninvasive procedure to minimize the main limitations found in the previously published studies, i.e. minimizing the effect of patient subjectivity in the analysis, as well as considering only those decisions derived from the analgesic state of the

patient. To test the algorithm, clinical data recorded from fifteen patients undergoing cholecystectomy surgery were considered. After the data preprocessing, different fuzzy inference systems were trained based on the methodology presented. A 4-fold cross validation was then applied to evaluate the resulting classifiers corresponding to the set of decision variables proposed in the study. Predictions achieved an accuracy in excess of 60% for all the set of inputs considered. In particular, accuracy was over 70% for most of the combinations proposed. To test the capability of predicting drug increases, the sensitivity was also studied. Four of the classifiers analyzed achieved a sensitivity value greater than 0.8. After comparing the different proposals, it was observed that the classifier trained with the average of the last 5 samples of ANI_m (ANI_{m5}) and the increment of the last 20 samples of ANI_i (ΔANI_{i20}) outperformed the other proposals. This FIS was formed by four- and two-input membership functions for ANI_{m5} and ΔANI_{i20}, respectively. The output of the FIS resulted in a value ranging from 0 to 100 to determine a decrease or increase in the infusion rate. An accuracy of 75.41% and an AUC of 0.8557 were finally attained by the fuzzy system.

The performance of the FIS proposed was classified as good regarding the AUC score [213]. A similar performance has been reached when using machine learning algorithms for drug dosage in medicine [214]–[216]. In addition, unlike previous proposals for developing a FIS from a decision tree [68], [217], [218], this method resulted in a fuzzy classifier with no limitation in the number of inputs. The main limitation of this work, however, was that only decisions based on increasing or decreasing the infusion rate were considered for the analysis of the ANI monitor. Further research should consider all the possible situations during the analgesia assessment.

Machine-learning-based method for evaluating the Analgesia Nociception Index in the assessment of general anesthesia

Considering the promising results presented in the previous study, and in order to address the main limitations found, a more detailed analysis was conducted to evaluate the ANI monitor. To this end, a machine learning approach was proposed. After the data acquisition and preprocessing, the SVM algorithm achieved the best classification results regardless of the input combination used for the training dataset. In particular, combining features involving both

hemodynamic information and minimum ANI index-derived features outperformed those decisions based only on non-specific clinical signs. The resulting SVM classifier performance (expressed as mean ± SD) was: accuracy: 86.21% (83.62%-87.93%), precision: 86.11% (83.78%-88.57%), recall: 91.18% (88.24%-91.18%), specificity: 79.17% (75%-83.33%), AUC: 0.89 (0.87-0.90) and kappa index: 0.71 (0.66-0.75). A median kappa index of 0.71 made the classifier a good tool for prediction [219].

In general, the resulting classifier hit 76% of the dose changes made by the anesthesiologist with a success rate of 90%-100% regardless of the fold partition considered for the training. Despite these promising results, there were some situations in which the success rate was lower than 60%. After a meticulous analysis, it was observed that considering both hemodynamic and ANI information could have prevented the hemodynamic reactivity detected in patients during the surgery. As a result, this monitor would help not only in the decision-making process, but also to predict and avoid errors throughout the process.

Finally, the performance of the trained SVM classifier was evaluated under the three different scenarios proposed. 96% of urgent dose changes were correctly predicted. In addition, 81% of those cases resulted in a posterior probability greater than 0.8. 84% of the non-urgent changes were correctly classified. In those situations in which the infusion rate was not changed, 62% of the records were predicted as increments or decrements of the dose with a posterior probability lower than 0.65. Thus, the current classifier was not confident enough to decide whether these records corresponded to an increment or a decrement of the remifentanil infusion rate. Taking these results into account, a three class-classifier based on the posterior probability criterion was synthesized. To this end, a prediction resulting in a posterior probability lower than 0.65 was considered as a “keep the dose” action. The new three-class classifier proposed resulted in an accuracy of 77% when predicting the different scenarios observed in the clinical practice.

The proposed solution based on a non-invasive scheme, together with a machine learning analysis of the results, constituted a novel approach to study the suitability of the monitor to report valuable information when replicating the actions of the anesthesiologists. Furthermore, it was observed that the ANI index may warn of the appearance of a hemodynamic event in the

next 10-15 min even if no hemodynamic changes were reported. Similar results were presented in [144], which showed the ability of ANI to anticipate hemodynamic changes in the next 5 minutes. In general, even though promising results have been presented, a higher number of records, including new situations and types of surgery, would enhance the analysis of the applicability of the ANI monitor for analgesia assessment.

4.2. Proposal of a *model* to study the effects of hypnotic and analgesic drug interaction on the DoH

Adaptive drug interaction model to predict depth of anesthesia in the operating room

The suitability of the algorithm proposed to identify the adaptive PK-PD patient models considering the propofol-remifentanil interaction, inter and intra patient variabilities, as well as the delay introduced by the BIS monitor, was evaluated with clinical data.

The identification algorithm was run throughout the different stages of the anesthetic process. During the induction phase, it was observed that the clinical response of the patient was satisfactorily described by the models identified. Maximum errors of PMSE = 61.06, MDPE = -4.18, and MDAPE = 9.34 were reported. During the maintenance phase, the identification was run every 11.63 (5.37) min to update the model according to the prediction error criterion defined in the methodology. Maximum prediction errors of PMSE = 143.41, MDPE = -14.05 and MDAPE = 17.01 were reported. Note that larger errors were obtained during the maintenance phase. While fitting errors were computed when comparing the output of the models with the same clinical data used for the identification during the induction phase, prediction errors were computed during the maintenance phase. To validate the results of the study, the identified parameters of the PK-PD models were compared with the ones presented in previous proposals. Similar values were obtained for both the induction and maintenance phases. The slight variations found could be due to the fact that the previous studies did not simultaneously take into account the effect of the drug interactions, patient variabilities, and the delay introduced by the BIS monitor.

Although the variations observed in the identified parameters among the different patients, as well as throughout the different stages of the process, evidenced the effect of the interpatient and intrapatient variabilities, the suitability of using an adaptive model was analyzed by comparing the prediction errors reported with those obtained by a non-adaptive strategy. Smaller errors and variations were observed when using the algorithm proposed to predict the DoH. This fact highlighted the importance of using an adaptive model for BIS prediction to deal with variations throughout the surgery.

4.3. Proposal of a robust optimal filtered PID *controller* for the DoH and comparison with a higher-order algorithm

Robust PID control of propofol anesthesia: uncertainty limits performance, not PID structure

The robust optimal filtered PID controllers were analyzed and compared with the Youla parameters. The PID controllers based on the three different scenarios proposed in the methodology were synthesized. Then, the individual Youla controllers were computed. Since a set of models was considered, the worst-case performance over the model set was optimized, while ensuring that each constraint imposed was satisfied for each model in the set. While optimizing mean or median performance constituted possible alternatives, the worst case was chosen here since it introduced safety through conservatism.

A high degree of similarity between the designs considered was observed when comparing the frequency response. The main difference between the individually optimized PID controllers and their Youla parameter counterparts lay in a phase advance in the mid-frequency range. The resulting optimization cost was then analyzed. Despite the additional degree of freedom provided by the Youla parametrization, Q design only improved the maximum cost achieved by the individual PID by 6%. Thus, very little room for performance improvement was observed when optimizing a Youla controller compared to an individually tuned filtered PID controller for a particular model. Including uncertainty from the interpatient variability, however, resulted in a significantly worse performance when comparing the distribution of the optimization cost over the patient models.

The different constraint levels considered for the optimization were also studied. Constraints on sensitivity and complementary sensitivity functions were not active regardless of the controller. The performance was limited by the constraint level on noise sensitivity in all the controllers except for that optimized for the additive uncertain model. This controller was limited by the undershoot constraint. Finally, the controllers were evaluated with the underlying non-linear models in a simulation. A DoH setpoint of $50\text{WAV}_{\text{CNS}}$ was considered. With the systems in stationary at this setpoint, a step disturbance was applied. All the designs provided admissible responses, minimizing the effect of the disturbance on the DoH. Expectedly, the robust controllers responded slower than the individualized ones.

Some other studies have proposed different objectives or synthesis problem formulations. In [220], a PID controller was optimized to limit the time to induce anesthesia, resulting in parameter values differing slightly from those reported in this study. In addition, a comparison between a PID controller and a higher-order model-based controller was conducted in [221]: however, both controllers were manually tuned. Thus, although the same design objective was considered for both controllers, different design criteria were eventually implemented. This is the first systematic comparison between a filtered PID controller and an optimal LTI controller for DoH control in which both structures were synthesized using the same performance criteria and robustness constraint.

5. Conclusions and future research

5.1. Conclusions

The automation of the anesthetic process has emerged as a common goal for clinicians and engineers. Although important advances have been achieved in recent years, the *total* automation of anesthesia remains a challenge. Considering the current problems in the field, this work has made contributions in three main areas: (i) the *assessment* of intraoperative analgesia by analyzing the Analgesia Nociception Index, (ii) the proposal of a *model* to study the effects of the hypnotic and analgesic drug interactions on the DoH, and (iii) the proposal of a robust optimal filtered PID controller and the main limitations introduced when comparing it with a higher-order structure for *controlling* the DoH. The main conclusions that can be drawn from this work are presented below:

- A novel scheme based on fuzzy logic techniques to study the suitability of including a new clinical variable into a decision-making process has been presented. This methodology resulted in a useful alternative when dealing with a lack of knowledge about a specific process since it is based on an automated algorithm.
- The fuzzy algorithm proposed was successfully applied to study the ANI monitor to assess analgesia during general anesthesia.
- The use of machine learning algorithms to evaluate the suitability of the ANI monitor when guiding analgesic drug delivery showed that considering this variable would improve the decisions made based solely on non-specific clinical signs.
- The development of an adaptive structure to model the effect of the propofol-remifentanil interactions on the DoH outperformed the predictions obtained when considering non-adaptive models due to the effect of the inter and intrapatient variabilities in the anesthetic process.
- The synthesis of an optimal robust filtered PID to reduce the effects of the surgical stimuli on the DoH while dealing with uncertainty in propofol anesthesia was proposed.
- Given clinically imposed requirements on robustness in combination with representative interpatient variability, increasing the controller order beyond that of a filtered PID controller does not significantly increase the achievable performance in propofol DoH control.

The individual conclusions drawn in each publication included in the compendium are presented below:

A novel methodology to synthesize a fuzzy-based decision system to evaluate the introduction of a new variable in a decision-making process is published in Appendix A - I. This methodology consisted of defining a whole procedure: from recording the clinical data, to designing a fuzzy inference system and validating it. This algorithm was specifically developed to deal with a lack of heuristic knowledge, as it was capable of automatically synthesizing a set of rules from a dataset. To test the effectiveness of this methodology, a preliminary study to evaluate the convenience of using the ANI index in analgesia was performed. Only increases and decreases in the drug dose were considered in the analysis. In light of the results, a fuzzy inference system based on the information in the last four samples of ANI_m and the variation in the last 20 samples of ANI_i was capable of replicating most of the decisions included in the study. These promising results spurred a more detailed study on the applicability of the ANI monitor to guide analgesic drug titration. Although this general methodology was originally thought to be applicable to the clinical field, this algorithm has also resulted in a useful tool when dealing with a lack of knowledge in the industry. Specifically, successful results have been achieved when using this methodology to automate a decision support system for production planning in industry [222].

In order to conduct a more detailed analysis to study the ability of the ANI to guide analgesic drug titration during surgeries, a machine learning approach is proposed in Appendix A - II. Unlike the previous published research, the main novelty of this analysis lies in a non-invasive methodology, free from subjectivity of the patient, to evaluate the ANI index. Thus, the suitability of the monitor was evaluated through its ability to provide valuable information to replicate the actions of the anesthesiologists during real surgeries. The results showed that (i) including data on the minimum ANI values recorded during the last 10 minutes outperformed those predictions based solely on hemodynamic information; (ii) the ANI may be capable of anticipating the need to change the dose before the appearance of a hemodynamic event and (iii) the resulting SVM classifier yielded accurate predictions under different situations commonly observed in clinical practice. Specifically, this study showed that the use of an SVM classifier based on the information displayed by the ANI monitor, together with the

hemodynamic activity of the patient, provided information to detect not only the need for a change of dose, but also to label an appropriate level of analgesia. This research constitutes a new step towards the development of a closed-loop solution for remifentanil titration during general anesthesia. Considering the conclusions drawn, a proposal for the potential variables likely to be included as feedback variables in closed-loop analgesia has been presented.

To model the effects of the propofol-remifentanil interaction on the DoH, a new optimization-based methodology to identify adaptive PK-PD models is proposed in Appendix A - III. In contrast to previously published research, the proposed method deals simultaneously with (i) both interpatient and intrapatient variabilities, (ii) propofol-remifentanil interactions, and (iii) variations in the time delay introduced by the BIS monitor. The aforementioned potential of using an adaptive strategy considering both intrapatient and interpatient variabilities was demonstrated. These promising results show that the proposed method could be implemented in MPC controllers for closed-loop strategies to outperform previously published research.

The design of robust optimal filtered PID controllers for propofol anesthesia is presented in Appendix B. A synthesis formulation producing robust controllers, capable of both minimizing the effect of the surgical stimuli on the DoH and handling the interpatient variability, is proposed. The performance limitations associated with using a filtered PID controller vs. a higher order controller represented though a Youla parameter were then analyzed. Taking the same clinical and technical considerations into account for the synthesis of the different controllers, the design of individual specific solutions resulted in only marginal differences in performance when comparing an optimal Youla parameter and its optimal filtered PID counterpart. The interpatient variability is much more detrimental to performance than the limitations imposed by the simple structure of the filtered PID controller. Thus, there is little to gain by increasing controller complexity, unless model uncertainty stemming from interpatient variability is reduced.

5.2. Future research directions

The main results and conclusions presented in this thesis will motivate new future work aimed at the *total* automation of the anesthetic process. Furthermore, the methods presented can be applied to other scenarios, proposing new solutions to different problems. Specifically, some of the possible research directions to be undertaken in the future are presented:

- Extrapolate the scheme for introducing new variables in a decision-making process in new scenarios. In view of the results presented in this research, and taking into account that the general structure of the scheme is compatible with a wide variety of processes, the possibility of using a similar conceptual scheme in new problems arises. This will include not only the clinical setting, but also other scenarios where the reliability of a new variable in a decision-making process must be evaluated.
- The scheme presented could be applied to study other commercial devices for monitoring analgesia. Thus, a comparison between the different commercial variables to guide analgesic drug titration could be carried out.
- Analyze the capability of the fuzzy-logic-based scheme presented as a method for knowledge formalization in novel processes, or in those where extracting the heuristic knowledge manually is unfeasible. Thus, a standard method to obtain a set of rules easily interpretable for experts would be generated.
- Develop a machine learning system based on the solution presented in this thesis, including new clinical cases, to address all possible scenarios observed in the operating room as a preliminary step to a clinical test. This study will allow for the design of a complete decision support system for analgesic drug dosing in the anesthetic process. In addition, it can be used to complement the information for the interpretability of the ANI as a guide variable for drug titration.
- Conduct a clinical test for the decision support system proposed. This test must also include a comparison of the results obtained with a control group to validate this new system for remifentanil titration in anesthesia.
- Based on the results of the clinical validation, propose a controller for closed-loop titration of remifentanil during general anesthesia. Based on the main features of the

problem, the initial designs could include event-based strategies or even fuzzy algorithms.

- Implement an MPC controller to regulate hypnosis considering the new identification algorithm proposed to model the effect of drug interactions in anesthesia.
- Analyze the pharmacological characteristics of the patients to propose a classification based on their clinical response to drugs. This will require the application of the model presented over a larger population set. On the one hand, this will allow an in-depth analysis of the pharmacological characteristics of the patients. On the other hand, patient clustering based on the pharmacological response to drugs will promote a more individualized drug titration, and thus reduce the effect of interpatient variability.
- Clinical validation of the robust optimal filtered PID synthesized in this thesis to validate its feasibility in the operating room. In addition, new clinical results will complete a more practical comparison against other types of closed-loop controllers previously published.
- Propose robust optimal filtered PID controllers adapted to the different groups of patients classified according to their pharmacological characteristics. To this end, the identification algorithm presented in this thesis could be combined with the optimization technique for PID synthesis applied to each cluster of patients.
- Apply the methodology presented for synthesizing a robust optimal filtered PID controller to other clinical scenarios with similar technical and clinical requirements. In particular, this algorithm could be applied to synthesize closed-loop controllers for drug dosing in hemodynamic control.

In general, the development of these future research directions will constitute a great advance toward the *total* automation of the anesthetic process. In this sense, the success of the above proposals would finally lead to the development of a MIMO structure capable of simultaneously supplying the different drugs involved in anesthesia, making accurate decisions based on the anesthetic state of the patient, and optimizing the use of clinical resources.

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Appendix A. Published works

Appendix A – I. A novel fuzzy algorithm to introduce new variables in the drug supply decision-making process in medicine

This Appendix presents the first paper included in the compendium of publications. A novel scheme for assessing the suitability of introducing a new clinical variable in a decision-making process is proposed. In addition, this general scheme is contextualized to the analgesia assessment scenario where the Analgesia Nociception Index monitor was studied.

Title:	A novel fuzzy algorithm to introduce new variables in the drug supply decision-making process in medicine.
Journal:	Complexity
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Year:	2018
DOI:	10.1155/2018/9012720
Journal Impact Factor (2018):	2.591
Rank (2018):	21/105 – Q1 (Mathematics, interdisciplinary applications)

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Complexity
Volume 2018, Article ID 9012720, 15 pages
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Research Article

A Novel Fuzzy Algorithm to Introduce New Variables in the Drug Supply Decision-Making Process in Medicine

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One of the main challenges in medicine is to guarantee an appropriate drug supply according to the real needs of patients. Closed-loop strategies have been widely used to develop automatic solutions based on feedback variables. However, when the variable of interest cannot be directly measured or there is a lack of knowledge behind the process, it turns into a difficult issue to solve. In this research, a novel algorithm to approach this problem is presented. The main objective of this study is to provide a new general algorithm capable of determining the influence of a certain clinical variable in the decision making process for drug supply and then defining an automatic system able to guide the process considering this information. Thus, this new technique will provide a way to validate a given physiological signal as a feedback variable for drug titration. In addition, the result of the algorithm in terms of fuzzy rules and membership functions will define a fuzzy-based decision system for the drug delivery process. The method proposed is based on a Fuzzy Inference System whose structure is obtained through a decision tree algorithm. A four-step methodology is then developed: data collection, preprocessing, Fuzzy Inference System generation, and the validation of results. To test this methodology, the analgesia control scenario was analysed. Specifically, the viability of the Analgesia Nociception Index (ANI) as a guiding variable for the analgesic process during surgical interventions was studied. Real data was obtained from fifteen patients undergoing cholecystectomy surgery.

1. Introduction

Artificial Intelligence (AI) plays an important role in science and engineering. This methodology is able to make decisions after a training process based on learning from a dataset obtained through expertise. One of the possible definitions of Artificial Intelligence refers to cognitive process and, specifically, to reasoning. Consequently, there is a natural relationship between Artificial Intelligence and decision-making [1]. Great progress has been made in different fields as industrial engineering [2, 3], tourist sector [4, 5], or energy field [6].

Specifically, in medicine, AI techniques have been applied with different aims. It includes the capability of learning automatically from data to control the health management systems, including an active guidance of clinicians in their treatment decisions. For clinical decision support, the key idea of the training process is extracting the expert knowledge form the

Abstract

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Specifically, in medicine, AI techniques have been applied with different aims. It includes the capability of learning automatically from data to control the health management systems,

including an active guidance of clinicians in their treatment decisions. For clinical decision support, the key idea of the training process is extracting the expert knowledge from the information concerning medical records and the unstructured data including natural language [7]. E-health systems have become popular as they automatically evaluate the situation of patients without involvement from a physician [8]. Decision-making process in hospital management for prioritization of risks and assessment of failures has been also approached [9, 10]. Moreover, AI has been used to automatic diagnosis and classification of illness [11, 12] and also for medical sensors fault detection [13]. Specifically, in medicine, the classifiers proposed to support a decision-making process must be suitable for being understood and evaluated from a clinician point of view [14]. Fuzzy rule-based systems have been widely used in medicine as they consist of simple linguistic rules that relate concepts in a natural manner [15, 16].

One of the main challenges in medicine is related to personalising the drug dose according to the real needs of patients. In most cases, the information obtained from the variable of interest leads to an increment or decrement of the drug infusion according to the medical criteria. AI has been also applied to automate the administration of drugs in medicine [17–20]. Important results have been reached in vasopressor administration [21, 22] or control of anaesthesia [23–26]. The key idea of these systems is a closed-loop scheme in which a controller decides the drug dose comparing the information of the measured variable to the proposed target. To design an appropriate control structure, it is necessary to deal with a well-known process. As a result, it is difficult to automate those processes in which the control variable cannot be easily measured or the relationship between the drug infusion and the effects on patient is not well established.

Nowadays, different clinical monitors are being developed in order to propose new variables to improve the decision-making process in medicine. However, trying to establish a strict criterion to correlate the new information with the physician's action based on traditional clinical variables is not an easy task. The main objective of this research was defining a novel general methodology capable of studying the feasibility of a new clinical variable (controlled variable) to guide the drug delivery process and then designing automatically a fuzzy-based decision system taking this new information into account. Firstly, the accuracy of the new

monitor to guide the drug infusion should be analysed. Then, the relationship between the new measurement and the physician criteria based on their expertise can be automatically proposed. The resulting Fuzzy Inference System based on a set of rules and membership functions makes it possible to obtain an easily interpretable drug delivery protocol for the clinician. A four-step methodology was proposed.

(i) Data collection for training process.
(ii) Preprocessing and analysis of data.
(iii) Designing the Fuzzy Inference System through a decision tree algorithm.
(iv) Validation of the results obtained.

There are different possible scenarios in which our algorithm could be applied. Specifically, to test the methodology above, the analgesia drug delivery process was analysed. Although different commercial monitors have been proposed, the main problem for the analgesia control is the absence of a reliable monitor to measure pain in patients undergoing surgery [27, 28]. In this research, the suitability of the Analgesia Nociception Index (ANI) to guide the analgesic process under surgery was analysed. Training data were obtained from 15 patients undergoing cholecystectomy surgery. The paper is organised in the following way. The next section presents a detailed problem description as a starting point for this research. Section 3 provides a detailed explanation of the methodology proposed in this paper. Section 4 presents the application of the methodology to the analgesia control field. Section 5 presents the results of the method. Section 6 includes the discussion of the results. Finally, in Section 7 we conclude the paper.

2. Problem description

Delivering an appropriate amount of drug according to the real state of patient is such a hard task in medicine. Generally, physician evaluates the current state of the patient by means of specific monitors or using different clinical signs. Then, they decide whether it is necessary to change the drug dose. It is important to use the appropriate concentrations of medications to optimize clinical outcomes in patients in various clinical situations [29, 30]. However, finding the variable that can be directly related to the effect of drug is not a trivial problem.

As a matter of fact, a new trend has been based on the proposal and development of new variables, techniques, and monitors capable of offering new information that may be included in the decision-making process. However, are these new measures directly related to the process involved? How could we define a new drug supply protocol in order to include this new information? These are the questions that this research aims to answer. As a result, the main objectives of this paper are as follows:

1) Determining not only if the new controlled variable is able to guide the drug supply process but also which information should be specifically considered.
2) Defining a rule-based decision system in order to guide the supply process taking the new information into account.

Actually, there are a lot of fields in which the development of this algorithm would result in a success: glucose monitoring [31, 32], anaesthesia [33], or therapeutic drug monitoring [34, 35]. In this research, we have focused on the control of analgesia. Optimizing the dose of opioid may limit the risk of overdosing, the risk of post-operative hyperalgesia and may reduce the time of recovery after surgical procedure [36]. However, the evaluation of analgesia and, therefore, the nociception-antinociception balance during surgery is a challenge to address due to the absence of an objective measure for monitoring analgesia. Traditional methods for supplying opioids use nonspecific and nonsensitive methods based on simple changes in vital signs such as movement, tachycardia, or lacrimation [28]. Recently, different monitors have been developed for measuring analgesia during clinical interventions proposing different information as nociception measures: heart rate information [37], electromyogram [38], electroencephalogram [39], or electrical skin conductance [40]. Nevertheless, the reliability of these monitors has not been deeply studied in clinical practice to assert that there exists a variable directly related to analgesia [27, 41].

Analgesia Nociception Index is a measure based on Heart Rate Variability (HRV) analysis. HRV has been shown in several studies to measure Autonomic Nervous System tone, strongly influenced by anaesthetic drugs [42]. ANI has been employed in several research in order to validate it as a device capable of measuring the nociception balance [43–46]. ANI seems more sensitive than other traditional measures based on hemodynamic response of patient under

propofol interventions to moderate nociceptive stimuli [47]. Using the ANI monitor as a guidance variable for analgesic titration may reduce the time recovery after the intervention, as well as the consumption of the analgesic agent [48, 49]. Moreover, ANI may enable consistent reflection of stimulation during propofol-remifentanil anaesthesia, improving detection of a possible inadequate nociception/antinociception balance [50].

For conscious patient, the sympathetic-parasympathetic balance is affected by psychological stress. Using ANI in this case does not exclusively detect nociception but may be modified by stress and emotion [51, 52]. In general, further research is needed to evaluate whether ANI is a tool able to provide beneficial effects to the patients during anaesthesia. Traditional studies tend to compare ANI information with postoperative patient's painful experience to validate the ANI monitor. Visual Analogue Scale (VAS) is a standard measurement tool in pain research and clinical practice [53, 54]. It is supposed that changes in VAS score represent a relative change in magnitude of pain sensation. However, trying to establish a correlation between the ANI index during surgery and the postoperative evaluation of pain through VAN is influenced by pain subjective experience of patients [55]. Another trend is studying the variation of the monitor's measure through the application of painful stimuli to the patient [56], a clinical practice that may damage the patient's health. As a result, more research is needed to find a feasible method to test the validity of the different alternatives proposed. Although no analytical relationship has been proposed between drug infusion and ANI index, very promising results have been reached when using ANI as guidance variable in analgesia [57, 58]. The algorithm developed in this research will be applied to propose a new solution to the analgesia problem from the AI point of view.

In light of the above, applying the novel algorithm proposed in this research to the control of analgesia will result in

(i) Determining whether the information displayed by the Analgesia Nociception Index is suitable to guide the analgesic process.
(ii) Defining a Fuzzy Inference System considering the information displayed by the ANI capable of predicting the actions of the clinician.

3. Methods

In the present study, decision trees as well as fuzzy logic techniques were used. The basis of these algorithms is introduced in the following subsections. The main idea was using the information of a decision tree to design a Fuzzy Inference System (FIS). This structure will be capable of predicting the expert's decisions after a training step based on real data when a new monitor is involved in a drug supply process. Although more recent machine learning techniques have emerged with the purpose of the automation of data analysis, fuzzy logic has been chosen in this study for several reasons. Firstly, most of medical decisions when changing the drug dose cannot be based on crisp values or strict predefined criteria. Thus, fuzzy values due to the presence of ambiguous concepts in the decision-making process such us interpatient variability or the existence of a lack of knowledge behind the process are required. That is why using membership functions in order to define the different categories for the decision variables seems to be the most appropriate option for the decision-making process. On the other hand, fuzzy logic is a well-known method able to easily relate the heuristic knowledge to a set of rules in a natural manner. What is more, no complex mathematical modelling is needed as it is based on a linguistic characterisation of the quality of the controlled process. Obtaining a Fuzzy Inference System automatically through the algorithm we propose will result not only in the development of an automatic system for the drug supply trained with real data, but also in the definition of the basis of the process by means of a set of rules easily interpretable for clinicians.

The general scheme of the method proposed to design the decision-making system is shown in Figure 1. One of the key steps in this methodology is the data collection. Data displayed by the new monitor must be recorded in parallel to the traditional drug supply process. It is important to note that the new monitor involved in this process should compute a numerical index in order to be able to apply the novel algorithm. To avoid conditioning the expert decision, the new information displayed must be hidden. Then, a preprocessing step is performed. Several proposals of the input data including different characteristics of the new measure must be considered. A decision tree algorithm is trained using the data recorded. The rules obtained will be the base to design the Fuzzy Inference System to predict the dose changes. On the one hand,

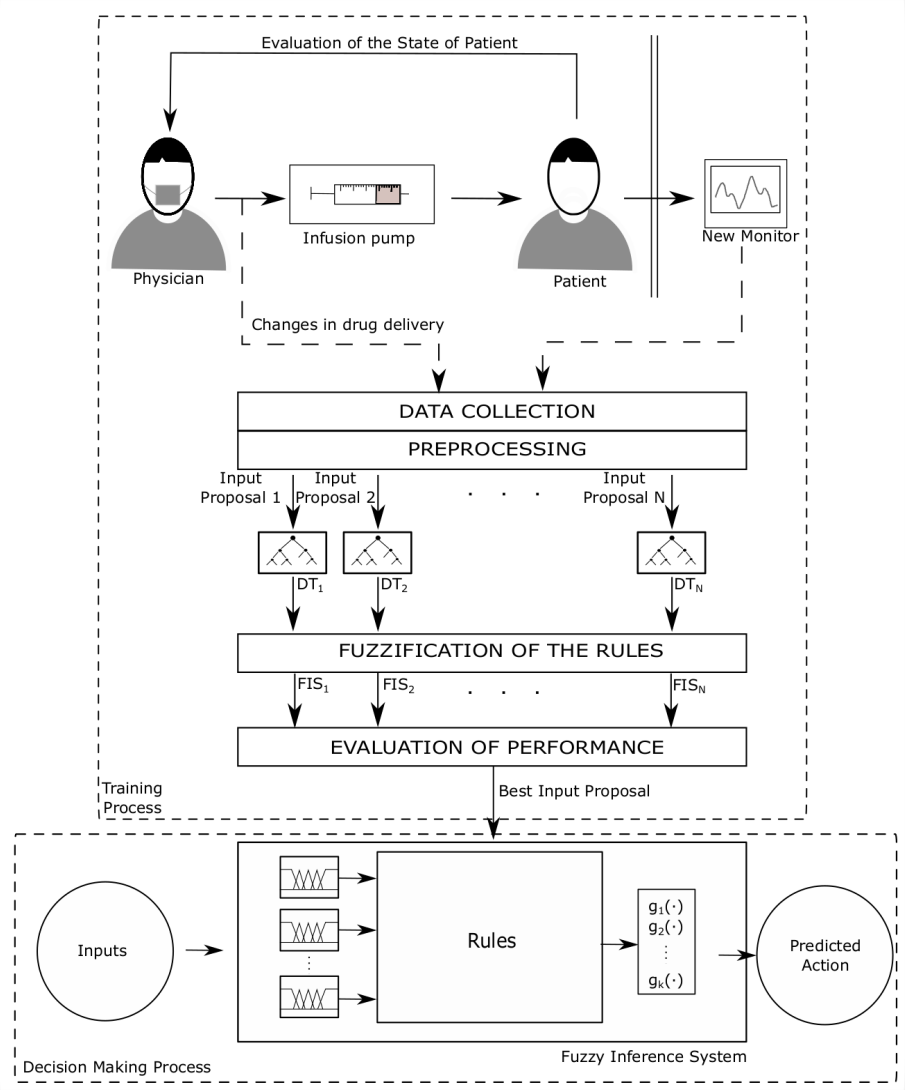

Figure 1. General scheme of the algorithm proposed in this study.

it is possible to study the performance of the algorithm when trying to relate the new measure to the physician's actions. As a result, a first approach of the reliability of the new measure to

guide the drug supply can be reached. Moreover, it is possible to determine which input proposal fits better to the decision-making process. On the other hand, the resulting Fuzzy Inference System consists of a set of rules whose interpretability improve the "user-friendliness" of the drug delivery protocol.

3.1. Decision Tree

Decision tree is a supervised machine learning algorithm able to build a model that makes predictions based on a known set of input data and known responses (output). The goal is to assign a class (categorical variable) from a finite set of classes to an observation. The decision tree consists of tests nodes linked to two or more subtrees and leafs or decision nodes labelled with a class which means the decision [59]. An instance is classified by starting at the root node of the tree. If the node is a test, the process continues with one of the subtrees. On the other hand, when a leaf is reached, the instance is classified with the correspondent label. An attribute node has exactly as many branches as its number of different value classes. Different algorithms to induce decision trees have been proposed [60, 61]. The main idea relies on using statistical calculation of information gain from the attributes. As a result, attributes adding the most information about the decision are selected first in the decision tree construction.

For this research, a CART (Classification and Regression Trees) algorithm was proposed. This method introduced by Breiman et al. [62] is focused on minimising the relative sum of squared errors in the two partitions resulting from a split. Generally, a two-step process is developed: a preliminary induction of the model through a training set under the "divide and conquer" principle and a checking process of the accuracy from a testing set. The search for splits in CART is based on two main characteristics: the covariate to split on and splitting point within that covariate [63]. Firstly, trees are grown to a maximal size stopping when no further splits are possible due to the lack of data [64]. Gini, similar to entropy criterion, is used as the splitting rule for classification. For a two-decision target the Gini measure of impurity of a node *t* is given by the expression below.

$$G(t) = 1 - p(t)^2 - \big(1 - p(t)\big)^2, \quad (1)$$

where *p(t)* is the relative frequency of one of the labels in the node. Then, the tree is pruned back to the root based strictly on the training data according to a cost-complexity measure defined as

$$Ra(T) = R(T) + a|T|, \quad (2)$$

where *R(T)* is the training sample cost of the tree, $|T|$ is the number of terminal nodes, and *a* is a penalty imposed on each node increasing from 0 to a value sufficient to prune away all splits. As a consequence, the next split to be pruned is the one that decreases the total performance of the tree.

3.2. Fuzzy Inference System

Fuzzy Inference System (FIS) is a fuzzy logic based structure capable of making decisions in real time taking human expert knowledge into account. The main idea is based on mapping the inputs and the outputs through a set of predefined rules that involves the heuristic knowledge. According to fuzzy sets theory, each variable (input or output) is defined through a linguistic variable $\tilde{u}_i$ whose value can be described through linguistic values $\tilde{A}_i^j$ belonging to a universe of discourse U_i. Unlike crisp values, the values of the universe of discourse "belong to" a linguistic value in a certain degree [0,1] described by a membership function $\mu(u_i)$.

$$\mu_{A_i^j}(u_i) = X \rightarrow [0,1]. \quad (3)$$

A value near 1 indicates that the value is almost fully in the set. A fuzzification process is necessary to turn crisp values to a fuzzy value. The singleton fuzzification is the most commonly used method. Then, the mapping of the inputs to the output is characterised by *if-then* rules. An inference step is needed to obtain conclusions from inputs and rule base. In this study, a Takagi-Sugeno inference system was developed.

$$\text{IF } u_1 \text{ is } A^1{}_i, \text{ AND } u_2 \text{ is } A^2{}_i, \text{ AND } \ldots \text{ and } u_n \text{ is } A^n{}_i, \text{ THEN } b_i = g_i(\cdot), \quad (4)$$

here "·" represents the argument of g_i function. As a result, the consequent of a Takagi-Sugeno inference is a function that may include the input terms u_i. Finally, a defuzzification method is needed to obtain a crisp value of the output:

$$y = \frac{\sum_{i=1}^{R} b_i \mu_i}{\sum_{i=1}^{R} \mu_i}. \quad (5)$$

The general structure of a Fuzzy Inference System is shown in Figure 2.

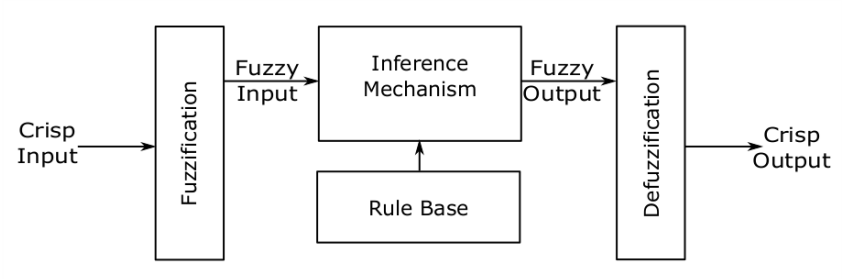

Figure 2. General structure of a Fuzzy Inference System.

3.3. Fuzzification of the Decision Tree Rules

Generally, when a decision must be made in medicine, there is not a predefined universal criterion. It is mainly due to the different inter and intravariability characteristics that the process involves. As a result, it does not make any sense to consider a crisp value as a strict limit to make a decision. That is one of the main reasons why a FIS was introduced in this research. Furthermore, fuzzy logic is based on "categories" or membership functions easier to interpret for clinicians as it groups information with similar characteristics for the decision-making process.

One of the key steps when designing a FIS is related to the definition of the membership functions and the rule base. It is especially difficult when there is not a deep heuristic knowledge behind the process. To avoid this problem, a decision tree technique is proposed to obtain it automatically from real data. The limits of the membership functions will be defined through the conditions in the test nodes and the rules will inherit from it. However, while the limits of the decision tree are crisp values based on training data, fuzzy values are required for Fuzzy Inference Systems. In addition, when the number of training and testing data is limited, it can turn into a harder problem. In order to generalise our model and to take advantage of the fuzzy

techniques, triangular and trapezoidal membership functions were used for intermedia and edge partitions of the universe of discourse, respectively. Moreover, we proposed to increase the limits of each membership function in 10% to get an overlap and avoid problems related to the limitation in the amount of data in the training step. The new limits for each membership function are calculated as shown below:

$$New\ lower\ limit = lower\ limit - \frac{upper\ limit - lower\ limit}{2} \cdot 0.1 \quad (6)$$

$$New\ upper\ limit = upper\ limit + \frac{upper\ limit - lower\ limit}{2} \cdot 0.1. \quad (7)$$

The 2-step process for the fuzzification of the inputs is described in Figure 3.

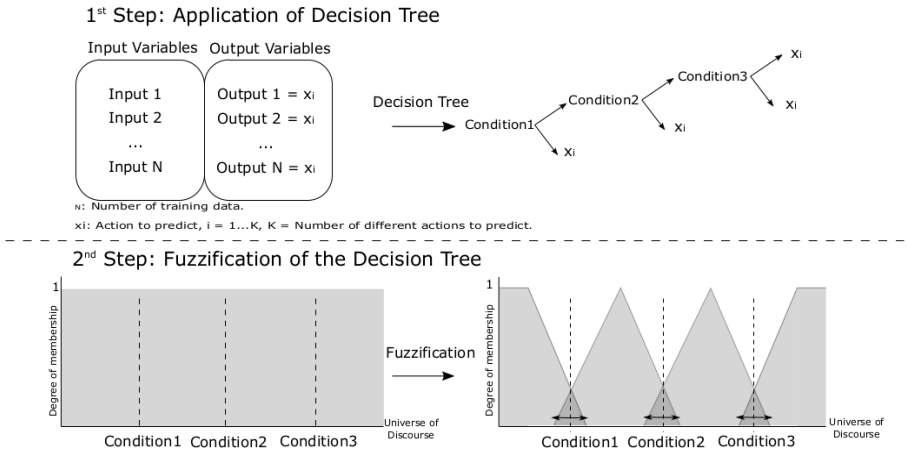

Figure 3. General structure of a Fuzzy Inference System.

Finally, the number of output functions matches the number of actions that the physician can handle. A constant function will be proposed for each action. For a general situation in which two decisions can be made (decreasing or increasing drug), a constant value of 0 and 100 could be associated with each action, respectively. In this case, the Fuzzy Inference System will calculate a number within the 0-100 range that could be considered as a percentage of action. A value of 50 could be regarded as the limit between both decisions.

3.4. Evaluation of the FIS decision maker

In order to evaluate the performance of the method proposed and the capability of the resulting Fuzzy Inference System to predict the decision-making process, a *k*-fold cross-validation must be performed [65]. The original sample is randomly divided into *k* equal sized subsamples. A single subsample is considered as the validation data for testing the Fuzzy Inference System, while the remaining *k*-1 subsamples are used as training data. The process is repeated *k* times varying the validation data and the results are averaged to obtain a single estimation. Different measures are calculated to study the performance of the classification [66]. The accuracy indicates the percentage of the dataset that are correctly classified by the proposed classifier. The sensitivity and specificity calculate the proportion of positive and negative records that are correctly classified, respectively. Precision refers to the fraction of relevant instances among the retrieved instances while recall is the fraction of relevant instances that have been retrieved over total relevant instances. The mathematical expressions to calculate the different measures are shown below.

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FN+TN} \cdot 100\ (\%) \tag{8}$$

$$\text{Sensitivity} = \frac{TP}{TP+FN} \tag{9}$$

$$\text{Specificity} = \frac{TN}{TN+FP} \tag{10}$$

$$\text{Precision} = \frac{TP}{TP+FP} \tag{11}$$

$$\text{Recall} = \frac{TP}{TP+FN}. \tag{12}$$

Given two classes, TP (true positives) refer to the positive records that have been correctly classified by the FIS, while TN (true negatives) are the negative records that have been correctly labelled by the classifier. On the other hand, FP (false positives) are the negative records that have been incorrectly labelled, while FN (false negatives) refers to the positive records incorrectly classified by the FIS. The confusion matrix to define the different measures is shown in Table 1.

Different input proposals based on different information from the new monitor are considered in the algorithm. In order to choose the best input proposal for the decision-making

	Predicted	
	Positive	Negative
Observed		
Positive	TP	FN
Negative	FP	TN

Table 1. Confusion matrix for positive and negatives records.

process, the evaluation of the input variables resulting in the highest accuracy, sensitivity, specificity, precision, and recall will be considered for the final FIS. To determine whether the information provided by a new monitor is relevant for a specific decision making-process, the measures of performance should be compared with the results obtained in similar previous research based on traditional decision methods or, if it was not possible, being evaluated by an expert.

4. Analgesia assessment application

This study has been approved by the Ethics Committee for the Clinical Research of the Hospital Universitario de Canarias (2014-97 (760954923-54923-4-14)). After obtaining written informed consent from patient, fifteen patients undergoing cholecystectomy surgery were enrolled in this study. A total intravenous anaesthesia (TIVA) with propofol (hypnotic) and remifentanil (analgesic) was performed for induction and maintenance of general anaesthesia. A Bispectral Index (BIS) monitor (Aspect Medical Systems Inc., Newton, MA, USA) was used as guidance variable for propofol titration. The propofol dose was changed during the surgery to maintain BIS values between 40 and 60, with a target of 50. The target dose of remifentanil was adjusted at the discretion of the anaesthesiologist, according to clinical practice parameters, anticipation to surgical stimuli, reactivity, or hemodynamic events. The dose of remifentanil was adjusted in steps of 0.05-0.1 mcg kg^{-1} min^{-1}.

4.1. The Analgesia Nociception Index

The Analgesia Nociception Index (ANI), developed by Mdoloris Medical System, is a noninvasive system that displays a continuous index related to the Autonomic Nervous System

(ANS) through the heart rate variability. ANI is supposed to be a monitoring system of the parasympathetic activity that displays information about the level of pain or stress in patients undergoing surgery. ANI index computation is based on a frequency domain analysis of the ECG signal. The main idea leads to studying the spectral content of RR waves series after a preprocessing step focusing on the high frequency range only influenced by the parasympathetic tone. Specific ECG electrodes are placed on the chest or back of patient to collect the heart rate variability. Every second two measures ranging from 0 to 100 are displayed: instant ANI and mean ANI. Instant ANI is directly related to the reactions of the patient to painful stimuli while mean ANI, computed after two minutes of averaging instant ANI, is related to the effects of analgesia on a patient. As a result, instant ANI may detect the actions of the surgeon and mean ANI could be useful for the titration of analgesia. Target values between 50 and 70 for mean ANI have been proposed to avoid unwanted hemodynamic events. Values under 50 increase the possibility of hypertension, hypotension, tachycardia, or bradycardia events.

4.2. Data collection and preprocessing

According to the process described in *Methods*, the data collection is the first step of the proposed methodology. In this case, two anaesthetists took part in each surgery. One of them was in charge of the drug supply, while the second one supervised the data recording process in a computer. A software in Matlab was developed in order to collect the data automatically. The scheme of the process is shown in Figure 4. Information displayed by the ANI monitor was hidden in order to avoid conditioning the decisions of the first anaesthetist. Instant ANI, mean ANI, and remifentanil dose changes (mcg kg^{-1} min^{-1}) were recorded every five seconds. Predefined surgical stimuli were also registered: nasogastric tube, laryngoscopy, incision, trocars, and the creation of pneumoperitoneum.

A postoperative offline study was made to try to correlate the rate changes of remifentanil with the ANI values. Before the analysis, a data preprocessing was necessary. On the one hand, zero-index value because of poor signal or external disturbances was corrected through a linear interpolation algorithm. On the other hand, only changes of remifentanil due to the analgesic

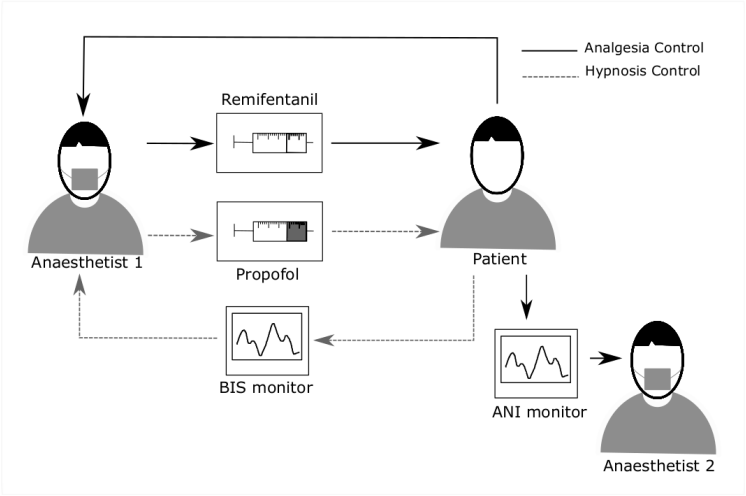

Figure 4. Scheme of the data collection process during the surgical interventions.

state of patients were considered in this study. Changes of remifentanil rate during surgery were based on two criteria: the anticipation to predefined painful surgical stimuli and the analgesic state of patient. As far as ANI is not able to predict the changes based on the anticipation to surgical stimuli, these values were not considered in this study.

4.3. Decision variables

The accuracy of the algorithm prediction will be directly related to the combination of the input-output variables proposed. As a result, different information obtained through the ANI index was tried to establish a relationship with the action of the anaesthetist. Firstly, a categorical variable was considered for the output. Consequently, "increasing drug" or "decreasing drug" labels were defined as it fully considers the anaesthetist's actions. Moreover, nonquantitative values of changes in remifentanil dose were analysed as the rate changes were limited by the clinical protocol (steps of 0.05-0.1 mcg kg^{-1} min^{-1}).

For the input, different variables computed from instant ANI and mean ANI were taken into account. In addition, the effects of considering different time intervals for both variables were also analysed. Finally, to study the evolution of ANI, the increment of instant ANI was

computed through the slope of the regression line that best matched the last values for a time interval. The variables proposed and their description are shown in Table 2.

Variables	**Description**
ANI_{i20}	Instant ANI of last 20 samples (100 s)
ANI_{m} and ANI_{i5}	Last mean ANI and last 5 samples of instant ANI (25 s)
ANI_{m5} and ANI_{i10}	Mean ANI of last 5 samples (25s) and instant ANI of last 10 samples (50s)
ANI_{m10} and ANI_{i20}	Mean ANI of last 10 samples (50 s) and instant ANI of last 20 samples (100 s)
ANI_{m10} and ANI_{i30}	Mean ANI of last 10 samples (50 s) and instant ANI of last 30 samples (150s)
Average ANI_{m5} and ANI_{i5}	Average of last 5 samples of Mean ANI (25 s) last 5 samples of instant ANI (25 s)
Average ANI_{m5} and ANI_{i20}	Average of last 5 samples of Mean ANI (25 s) last 20 samples of instant ANI (100 s)
Average ANI_{m5} and ΔANI_{i5}	Average of last 5 samples of Mean ANI (25 s) the increment of last 5 samples of instant ANI (25 s)
Average ANI_{m5} and ΔANI_{i20}	Average of last 5 samples of Mean ANI (25 s) the increment of last 20 samples of instant ANI (100 s)

Table 2. Description of the input variables proposed for the study.

5. Results

The decision-making methodology proposed was applied to the analgesic drug supply scenario. Fifteen patients undergoing cholecystectomy surgery were enrolled in this study. An example of the data collected during the interventions is shown in Figure 5. A total of 91 increasing/decreasing events were registered during the 15 surgeries. After discarding the changes due to the anticipation to painful stimuli, 53 events were finally considered for this study (32 increasing versus 21 decreasing).

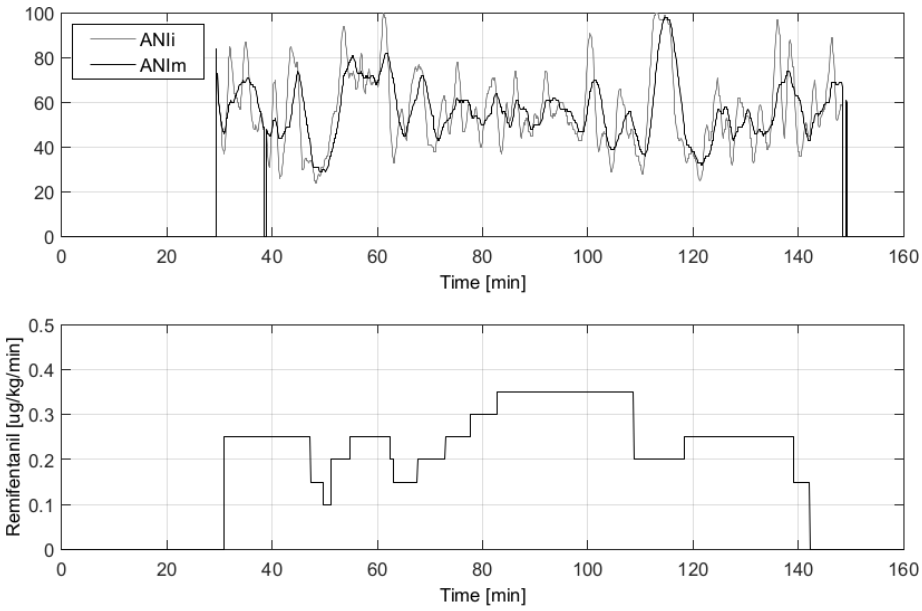

Figure 5. Example of the data collected for a patient undergoing cholecystectomy surgery. ANI registered (top) and remifentanil infusion rate (bottom). ANI_i: instant ANI. ANI_m: mean ANI.

5.1. Evaluation of the proposed variables

The performance of the resulting Fuzzy Inference Systems for both "increasing drug" and "decreasing drug" actions considering the different variables proposed in Section 4.3 is shown in Tables 3 and 4. A 4-fold cross-validation was applied for each combination according to the total number of training data.

In light of the results of the cross-validation, accuracy was over 60% for all the inputs considered. Specifically, accuracy was over 70% in most of the combinations proposed. Regarding the analgesia scenario, it was highly important to note that a low value of analgesia in patients can lead to complications and prolonged rehabilitation as well as the development of chronic pain with reduction in quality of life [67, 68]. Consequently, accurate increments of remifentanil dose were desirable. That was why sensitivity and recall measures in Table 3 were specifically considered to choose the appropriate FIS. In this sense, there were up to four input-output combinations that resulted in sensitivity and recall values over 0.8. Taking these four

Input	Accuracy	Sensitivity	Specificity	Precision	Recall
ANI_{i20}	71.57	0.83	0.65	0.80	0.83
ANI_m and ANI_{i5}	71.57	0.77	0.74	0.83	0.77
ANI_{m5} and ANI_{i10}	66.07	0.69	0.71	0.80	0.69
ANI_{m10} and ANI_{i20}	69.64	0.81	0.62	0.80	0.81
ANI_{m10} and ANI_{i30}	71.57	0.76	0.72	0.83	0.76
Average ANI_{m5} and ANI_{i5}	71.57	0.77	0.72	0.81	0.77
Average ANI_{m5} and ANI_{i20}	71.57	0.83	0.64	0.80	0.83
Average ANI_{m5} and ΔANI_{i5}	62.09	0.71	0.56	0.73	0.71
Average ANI_{m5} and ΔANI_{i20}	75.41	0.82	0.71	0.80	0.82

Table 3. Comparison of performance for the different input combinations for when applying the proposed algorithm for increasing drug action. Accuracy expressed as %.

Input	Accuracy	Sensitivity	Specificity	Precision	Recall
ANI_{i20}	71.57	0.65	0.83	0.5	0.65
ANI_m and ANI_{i5}	71.57	0.74	0.77	0.72	0.74
ANI_{m5} and ANI_{i10}	66.07	0.71	0.69	0.62	0.71
ANI_{m10} and ANI_{i20}	69.64	0.62	0.81	0.46	0.62-
ANI_{m10} and ANI_{i30}	71.57	0.72	0.76	060	0.72
Average ANI_{m5} and ANI_{i5}	71.57	0.72	0.77	0.70	0.72
Average ANI_{m5} and ANI_{i20}	71.57	0.64	0.83	0.51	0.64
Average ANI_{m5} and ΔANI_{i5}	62.09	0.56	0.71	0.62	0.56
Average ANI_{m5} and ΔANI_{i20}	75.41	0.71	0.82	0.74	0.71

Table 4. Comparison of performance for the different input combinations for when applying the proposed algorithm for decreasing drug action. Accuracy expressed as %.

combinations into account as well as specificity and precision values, it was concluded that the best performance was reached when considering the average of the last 5 samples of mean ANI and the increment of the last 20 samples of instant ANI. Similar results were reached when

analysing Table 4, as this input-output proposal resulted not only in the highest sensitivity-specificity combination but also in the highest precision value.

As a result, the last 5 samples of mean ANI and the increment of the last 20 samples of instant ANI were chosen for the input of our decision-making system. Regarding the performance reached, it was possible to affirm that there existed a relationship between the actions of the anaesthesiologist during surgery and the values displayed by the Analgesia Nociception Index.

5.2. Structure of the Fuzzy Inference System

Taking into account the comparison of performances in Section 5.1, the analysis and the result of the final FIS regarding the input-output proposal with the highest prediction score (the last 5 samples of mean ANI and the increment of the last 20 samples of instant ANI) are studied in this section. On the one hand, the decision tree obtained is shown in Figure 6. The value of the input variables proposed for the 53 registered events are shown in Figure 7.

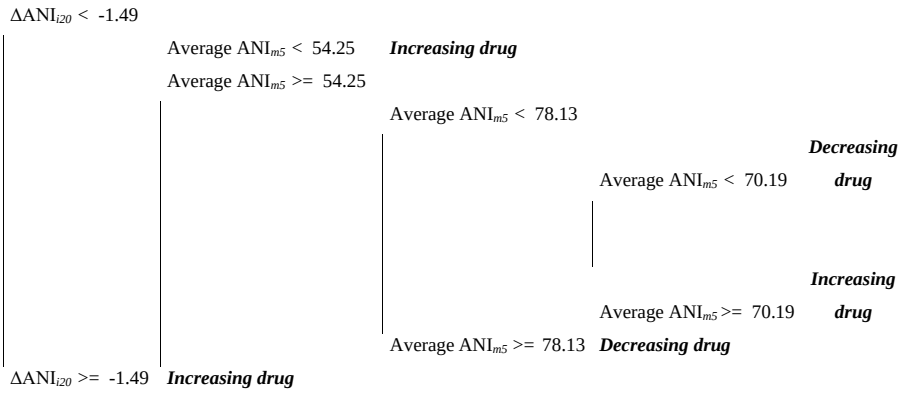

Figure 6. Decision tree obtained for the best input-output proposal (the last 5 samples of mean ANI and the increment of the last 20 samples of instant ANI) when applying the algorithm.

Triangular as well as trapezoidal membership functions were used for both inputs. The number of the membership functions were defined by the total number of test nodes associated to each input. The limits, inherited from the test node conditions, were fuzzified according to

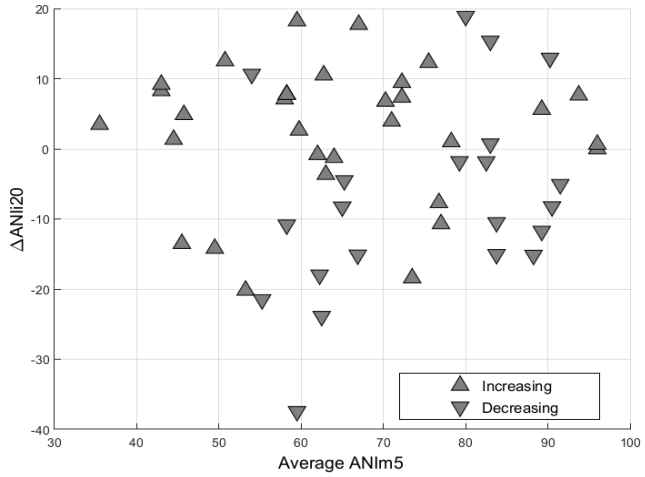

Figure 7. Value of average ANI_{m5} and ΔANI_{i20} computed for every remifentanil rate change (increasing drug or decreasing drug).

the criteria in Section 3.3. The results are shown in Figure 8. A number of four and two membership functions were defined for the average ANI_{m5} and ΔANI_{i20} inputs, respectively.

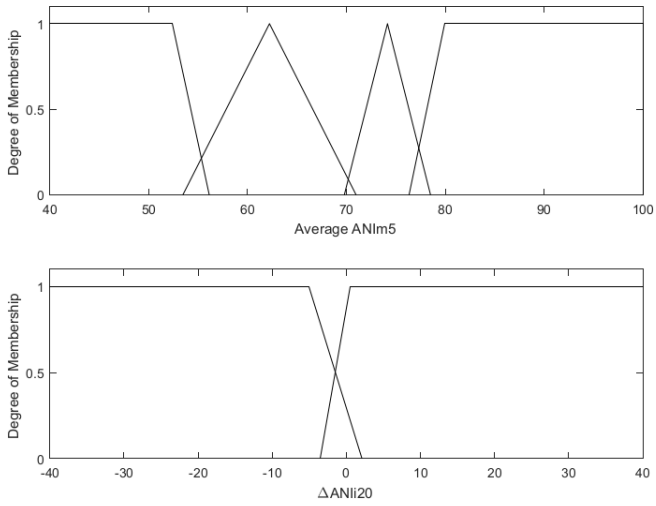

Figure 8. Input fuzzy partitions of the Fuzzy Inferences System. Top: membership functions for average ANI_{m5} input. Bottom: membership functions for the ΔANI_{i20} input.

Finally, the output functions of the FIS were defined. In this case, a two-decision system was needed: “increasing drug” and “decreasing drug” actions. Two constant output functions were proposed: “0” and “100” referred to the decreasing and increasing actions, respectively. As a result, the output of the FIS was a number within 0-100 range which could be regarded as a percentage of action. In this study, the results over 50 were considered as an “increasing drug” prediction while the values under 50 were considered as “decreasing drug” prediction. The fuzzy decision surface obtained and the comparison with the nonfuzzified decision tree surface are shown in Figure 9.

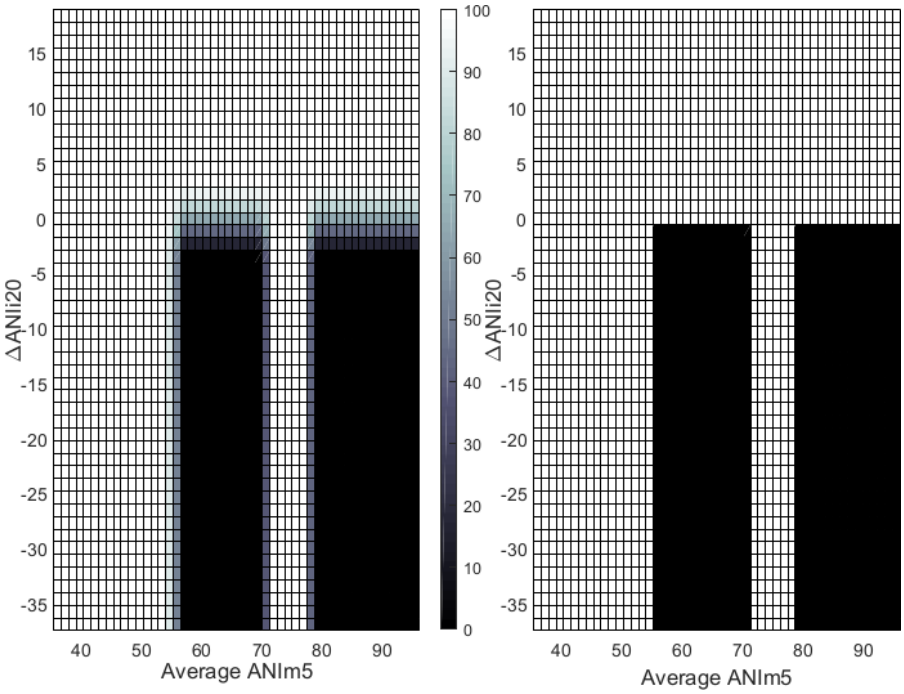

Figure 9. Comparison of the response surface for the Fuzzy Inference System (left) and for the decision tree (right). Output ranging from 0 (decreasing action) to 100 (increasing action).

To evaluate the performance of the FIS, the decision system was evaluated through a receiver-operating characteristic (ROC) curve by plotting the sensitivity, or true positive rate as a function of the false-positive rate. The ROC curves for both increasing and decreasing

predictions are shown in Figure 10. An Area Under the Curve (AUC) of 0.8557 was reached for the predictive model proposed.

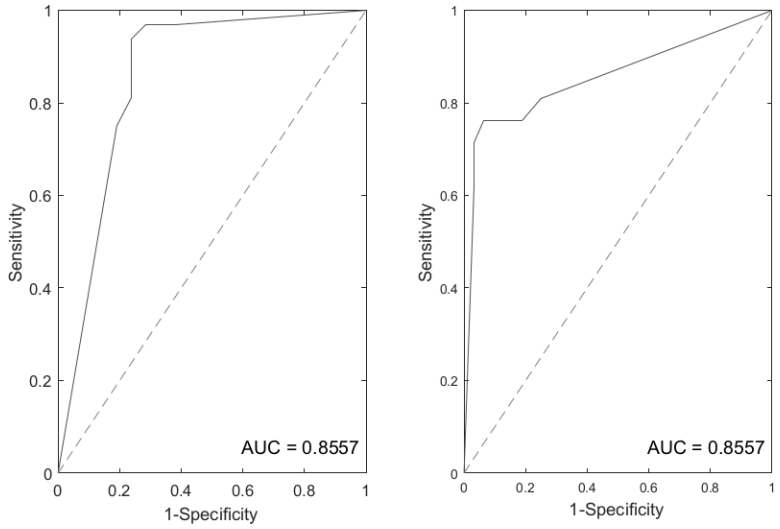

Figure 10. ROC curve showing the relationship between sensitivity (true-positive rate) and 1-specificity (true-negative rate) determining the performance of the FIS model proposed to predict the increments (left) and decrements (right) of remifentanil rate). AUC, Area Under the Curve.

Finally, the prediction of the Fuzzy Inference System developed for the 53 training data is shown in Figure 11.

6. Discussion

A new algorithm for the design of a computer-based decision system in medicine has been presented. Specifically, the application of the proposed methodology in this research has resulted in the development of a Fuzzy Inference System as a computer-assisted medical decision-making for the analgesia scenario. On the one hand, it was possible to determine that there existed a relationship between the Analgesia Nociception Index and the remifentanil supply during surgery. Particularly, the average of last five samples of mean ANI and the increment of last twenty samples of instant ANI reached an accuracy of 75.41%. Moreover,

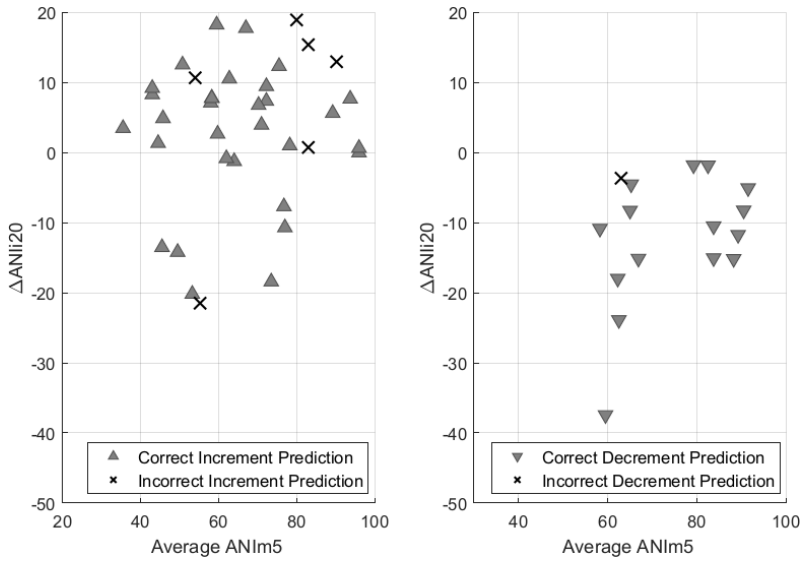

Figure 11. Prediction of the Fuzzy Inference System for increments (left) and decrements (right) of remifentanil rate.

sensitivity and recall values over 0.8 were reached when predicting the increments of remifentanil. Similar performance has been reached when applying different machine learning algorithms to optimize drug supply in medicine. Specifically, an accuracy ranging from 75% to 88% was obtained after a leave-one-out study when predicting the discrepancies between planned and delivered dose in proton therapy [69]. In [70], the overall predictive accuracy of the presented models for prediction of optimal cancer drug therapies was 80%. In the analgesia field, the development of models to predict the postoperative pain treatment reached an accuracy of 65% [71]. According to previous research, a clinically acceptable accuracy level is reached when applying our proposal. A two-input one-output FIS based on Takagi-Sugeno inference was developed. The resulting model reached an AUC of 0.8557 for both increasing and decreasing drug actions. As a result, the performance of the model to predict the actions of the anaesthesiologist may be classified as good [72].

From the Artificial Intelligence point of view, different approaches have been also proposed to fuzzy rule extraction from numerical data for classification [73-75]. However, the main novelty of this research is the definition not only of an automatic algorithm but also of the whole

process in order to evaluate the reliability of a monitor involved in a decision-making system. As far as we know, this is the first study that tries to establish a correlation between the information displayed by a monitor and the expertise-based decision-making process during surgical interventions. Consequently, it is possible to validate the accuracy of the device to drug assessment as well as to define a new drug delivery protocol. As a result, the knowledge behind the process is automatically built as a set of rules and categories or membership functions. On the one hand, this structure makes it easy to translate the knowledge into an interpretable language for clinicians. What is more, the output expressed as a percentage gives information about the decision and its reliability.

Merging decision trees with fuzzy logic has been previously proposed in order to handle uncertainty, ambiguity, and indeterminacy in the store information. However, unlike our method which results in a Fuzzy Inference System, the previous research has been based on fuzzy decision trees [76], [77]. They are mainly based on the use of decision tree whose nodes are not crisp values but membership functions. Bockstaller et al. proposed a new fuzzy decision tree for sustainability assessment [78]. They developed CONTRA tool to support the design of fuzzy decision tree. When using CONTRA, the user has to define the threshold and the limit values of each membership function in a previous step. Moreover, the choice of a weight or rank must be assigned to the different input variables in order to compute the output. Unlike our proposal, a previous heuristic knowledge is necessary in order to design the model. What is more, CONTRA tool limited the input variables to be aggregated between two and five in order to limit a maximum of thirty-two-decision rules. However, our method was able to work with an unlimited number of inputs.

One of the main limitations to this work is that the presented algorithm has been only applied to a two-decision system (increasing and decreasing drug) in analgesia. Further studies should be considered when applying this algorithm to another similar scenarios such as hypnosis, neuromuscular blockade, or glucose control. In addition, including this information to an automatic control system would be the first step in order to automate the analgesic process through a closed-loop strategy.

7. Conclusion

This paper introduced a new methodology in order to design a fuzzy-based decision system to improve the drug delivery process when a new guiding variable is involved. Furthermore, the capability of a new monitor to guide the drug titration can be analysed. This methodology involved the whole process: from the recording of numerical data computed by the new monitor to the design of the Fuzzy Inference System from real data. Fuzzy logic was used as it provides a well-understood mechanism for inducing classification rules from data and avoid possible problems related to the limitation of the number of training data. Rules as well as membership functions were extracted from a decision tree algorithm in order to automate the process. The algorithm proposed was tested in the analgesia scenario. In light of the results, it can be concluded that our method can be used to develop a decision-making system from real data in the medicine field although there exists a lack of knowledge behind the process.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Appendix A – II. Machine Learning based method for the evaluation of the Analgesia Nociception Index in the assessment of general anesthesia

This Appendix presents the second paper included in the compendium of publications. This paper aims to evaluate the suitability of the ANI monitor as a guidance variable to replicate the decisions made by an expert when a modification of the opioid infusion rate is required. Different machine learning classifiers were studied to this end.

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Machine learning based method for the evaluation of the Analgesia Nociception Index in the assessment of general anesthesia

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ABSTRACT

Measuring the level of analgesia to adapt the opioids infusion during anesthesia to the real needs of the patient is still a challenge. This is a consequence of the absence of a specific measure capable of quantifying the nociception level of the patients. Unlike existing proposals, this paper aims to evaluate the suitability of the Analgesia Nociception Index (ANI) as a guidance variable to replicate the decisions made by the experts when a modification of the opioid infusion rate is required. To this end, different machine learning classifiers were trained with several sets of clinical features. Data for training were captured from 17 patients undergoing cholecystectomy surgery. Satisfactory results were obtained when including information about minimum values of ANI for predicting a change of dose. Specifically, a higher efficiency of the Support Vector Machine (SVM) classifier was observed compared with the situation in which the ANI index was not included: accuracy: 86.21% (83.62%– 87.93%), precision: 86.11% (83.78%–88.57%), recall: 91.18% (88.24%–91.18%), specificity: 79.17% (75%–83.33%), AUC: 0.89 (0.87–0.90) and kappa index: 0.71 (0.66–0.75). The results of this research evidenced that including information about the minimum values of ANI together with the hemodynamic information outperformed the decisions made regarding only non-specific traditional signs such as heart rate and blood pressure. In addition, the analysis of the results showed that including the ANI monitor in the decision making process may anticipate a dose change to prevent hemodynamic events. Finally, the SVM was able to perform accurate predictions when making different decisions commonly observed in the clinical practice.

1. Introduction

Pain can be defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. The presence of subjective psychological aspects regarding pain makes it difficult to find efficient methods and techniques for pain measurement and treatment. It has been one of the main problems when trying to define general protocols for the delivery of analgesics. The absence of pain is specifically an important issue during surgeries, in which physicians should ensure an accurate level of analgesia. During anesthesia, nociception may be considered a pain measurement as it derives from the activation of nociceptors due to physiological processes [2]. One of the main trends in analgesia has been the evaluation of the nociception-antinociception balance. As a matter of fact, different devices have been recently presented as reliable tools to measure nociception [3].

Nowadays, however, there is not any accepted standard practice in order to supply analgesic drug during anesthesia. Traditional protocols for the delivery of opioids have been based on indirect signs, such as movement, presence of tachycardia, sweat or lacrimation [4]. As a result, the decision-making process during the anesthesia practice mainly relies on the expertise of the anesthesiologist. According to the US Institute of Medicine, 80% of patients who undergo surgeries report postoperative pain, even reaching extreme pain levels [5]. Inadequate levels of analgesia in patients undergoing surgery may result in risk of overdosing, risk of post-operative hyperalgesia and may increase the time of recovery after the surgery [6]. In addition, the presence of acute pain during surgery is related to the development of chronical pain [7].

Recent approaches for opioid titration have included the use of new monitors able to measure the nociceptive activity.

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Keywords: Anesthesia; Analgesia assessment; Analgesia Nociception Index; Machine learning; Opioid titration; Support Vector Machine.

1. Introduction

Pain can be defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [1]. The presence of subjective psychological aspects regarding pain makes it difficult to find efficient methods and techniques for pain measurement and treatment. It has been one of the main problems when trying to define general protocols for the delivery of analgesics. The absence of pain is

specifically an important issue during surgeries, in which physicians should ensure an accurate level of analgesia. During anesthesia, nociception may be considered a pain measurement as it derives from the activation of nociceptors due to physiological processes [2]. One of the main trends in analgesia has been the evaluation of the nociception-antinociception balance. As a matter of fact, different devices have been recently presented as reliable tools to measure nociception [3].

Nowadays, however, there is not any accepted standard practice in order to supply analgesic drug during anesthesia. Traditional protocols for the delivery of opioids have been based on indirect signs, such as movement, presence of tachycardia, sweat or lacrimation [4]. As a result, the decision-making process during the anesthesia practice mainly relies on the expertise of the anesthesiologist. According to the US Institute of Medicine, 80% of patients who undergo surgeries report postoperative pain, even reaching extreme pain levels [5]. Inadequate levels of analgesia in patients undergoing surgery may result in risk of overdosing, risk of post-operative hyperalgesia and may increase the time of recovery after the surgery [6]. In addition, the presence of acute pain during surgery is related to the development of chronical pain [7].

Recent approaches for opioid titration have included the use of new monitors able to measure the nociceptive activity during surgery. Different research has been conducted using the Analgesia Nociception Index (ANI) monitor [8–12]. This monitor makes a Heart Rate Variability (HRV) analysis to measure the effect of the Respiratory Sinus Arrhythmia (RSA). Very promising results have been reached when using the ANI monitor as guidance variable for opioids titration [9, 10]. A more sensitivity variable to stimuli and a lower drug consumption have been observed compared to traditional variables [13–15]. However, more research is needed to ensure the reliability of the ANI index for the analgesia management.

Considering the current problem in this field, the main objective of this research is the evaluation of the ANI monitor as a device capable of providing valuable information for the guidance of the analgesic drug titration during anesthesia. Particularly, unlike previous proposals, we present a new point of view to study whether it is possible to replicate the decisions of the experts in critical situations where a modification of dose is required. To this end, we have analyzed if the use of the ANI index in the decision making process can

outperform the assessment of opioids traditionally based on non-specific signs such as heart rate and arterial pressure. This research presents an evaluation of the performance reached by different machine learning classifiers to predict the changes of dose when including different features in the decision making process.

Regarding the main objective of the study, our hypothesis is that a variation in the remifentanil infusion rate evidences a bad analgesia level of the patient. Therefore, dichotomous qualitative variables representing “Increment of drug” and “Decrement of drug” decisions will be used for the data labelling. Then, the performance of the different predictors will be discussed. Finally, the performance of the synthesized two-class classifier will be analyzed under different scenarios observed in the clinical practice. Thus, unlike previous research, this study constitutes a new alternative for the evaluation of the ANI monitor, specifically focused on the decision making process for the analgesic drug titration. The presented methodology based on machine learning turns this approach into a first step towards the development of standardization of the analgesia management during anesthesia. Furthermore, this proposal could be considered for the development of oncoming intelligent controllers for the automation of analgesia.

1.1. Related works

Monitoring nociception is a challenge to lower the incidence of acute postoperative pain and the move towards a more automated approach to analgesia and anesthesia [16]. Main trend focuses on the development of new devices for the evaluation of the nociception-antinociception balance. These monitors claim a reduction of the postoperative pain together with a lower consumption of the analgesic drug compared with the traditionally used vital signs, including blood pressure and heart rate [17]. These devices are based on the detection of clinical signs related to the reaction to nociception. Among all commercially available options, the Analgesia Nociception Index has been widely studied in the clinical practice. Previous research aimed a clinical validation of the ANI monitor under different conditions. Some studies have been performed to evaluate the post-operative pain in awaken patients with the ANI monitor [18–20]. Pain intensity assessed in a 0-10 numerical rating scale by the patients has been compared with the measurement of ANI during the postoperative period. Some controversial

have been found when comparing the different studies. Main source of conflicts may come from the presence of arousal and emotions affecting the sympatho-vagal balance in awaken patients, constituting an important source of statistical artifact in the evaluation of pain intensity [21]. Including the subjective post-operative pain evaluation of the patient may constitute, therefore, a source of conflicts in this kind of studies.

To deal with this problem, the ANI monitor has been evaluated throughout the surgery. In [22, 23], the evolution of the ANI as well as heart rate and systolic blood pressure were recorded during the anesthetic process. Patients received tetanic stimulation to study the capability of the different clinical signs to reflect the nociceptive stimuli. The results evidenced opposing conclusions when evaluating the reactivity of ANI for the detection of the stimuli compared with other hemodynamic variables. Some other studies have resulted in inconclusive results when performing ANI-guided analgesia. Although the intraoperative opioid consumption was reduced, no effect was observed in the reduction of opioid-related side-effects [24]. In conclusion, no evidence exists for a clinically relevant benefit of ANI monitoring so far.

In light of the above, this research is not focused on the development of an algorithm for the automation of analgesia, but on a new point of view to overcome main difficulties found in previous research for the evaluation of the ANI monitor. Specifically, the main objective of this study lies in the evaluation of the Analgesia Nociception Index as a feedback variable to replicate the decisions of the clinician when an abnormal level of analgesia is detected. Thus, main novelties of the study are:

i) This proposal will not be based on a clinical validation of the ANI monitor as a tool capable of measuring the analgesic level, but on the analysis as a tool capable of providing valuable information when a change of dose is needed. This new scheme lies in the application of machine learning techniques for the analysis.
ii) The analysis is free from the subjectivity introduced by the post-operative evaluation of the patients. Unlike some of the previous proposals, only data recorded during the surgery involving both clinical variables and actions performed by the clinicians will be studied. As a result, the effects of arousal or emotions are diminished.

iii) The data acquisition process proposed in this methodology is not based on an invasive scheme. Instead of applying painful stimuli for the analysis of ANI as included in previous proposals, this study is fully based on the data obtained during real surgeries. Consequently, potential damage introduced by external painful stimulus is avoided.

2. Methods

2.1. Monitoring nociception: The Analgesia Nociception Index

The Analgesia Nociception Index (ANI) developed by Mdoloris Medical System [25], is based on the analysis of the parasympathetic component of the autonomic nervous system regarding the respiratory sinus arrhythmia. This is a consequence of a diminution of the RR intervals during inspiration. ANI uses specific electrocardiogram (ECG) electrodes placed on the chest or in the back to measure the heart rate variability. The spectral analysis of ECG results in a dimensionless score (0-100) displayed every second. ANI_i appears in yellow on the monitor and it is straightforward influenced by the reactions of the patients to the actions of the surgeon. Moreover, the monitor displays an additional value, ANI_m, which results from a two minutes averaging of ANI_i. ANI_m is supposed to be related to effects of analgesia on patients and, therefore, to be of interest for the titration of opioids. This device can be used with unconscious as well as conscious patients. For unconscious patients under general anesthesia, keeping ANI_m in the 50-70 range is related to an adequate analgesia, avoiding unwanted hemodynamic events. In case that ANI_m decreases below 50, hemodynamic reactivity in the next ten minutes has been observed. Finally, ANI_m values over 70 makes it possible to decrease opioids administration without any risk.

2.2. Clinical protocol and data collection

This study was approved by the Ethics Committee for the Clinical Research of the Hospital Universitario de Canarias. Written informed consent was obtained from the patients enrolled in the study. A Total Intravenous Anesthesia (TIVA) with propofol (hypnotic drug) and remifentanil (analgesic drug) was performed for induction and maintenance of general anesthesia. Two syringe pumps Graseby 3500 were used. Intravenous remifentanil infusion of

0.2 μg/kg/min started 7 min before induction. A propofol intravenous bolus of 1.5 mg/kg at the maximum syringe pump rate (1200 ml/min) was supplied. A Bispectral Index monitor (BIS) was used as guidance variable for propofol titration. The propofol dose was changed manually during the surgery to maintain BIS values between 40-60, with a target of 50. Remifentanil dose was adjusted by the clinician as a consequence of the hemodynamic response, defined as the variation of more than 20% of the heart rate (HR) and/or blood pressure (BP) for five minutes. Additionally, the anesthesiologist could change the remifentanil dose to prevent the effects of surgical stimuli during the process. Changes of remifentanil up to 0.05-0.1 μg/kg/min were allowed. Further details for remifentanil drug titration in anesthesia can be found in [26]. The clinical protocol also included a post-operative evaluation of the patients. This evaluation consisted of detecting postoperative complications related to the opioid administration such as nausea, vomiting, shaking or fatigue, the needs of dosing any other drug to minimize analgesia effect, or the time spent in Post-Anesthesia Care Unit (PACU).

To obtain the dataset for the analysis, information about remifentanil dose, heart rate, blood pressure and ANI were recorded during the surgery. For HR and BP monitoring, BeneView T8 or iPM 12, both developed by Shezhen Mindray Bio-Medical Electronics Co., were used in this study. Non-invasive blood pressure cuffs (NIBP) and ECG electrodes and cables compatible with the monitors were used for BP and HR respectively. The use of one monitor or the other depended on the availability in the operating room scheduled for the surgery. For the Analgesia Nociception Index monitoring, ANI monitor developed by Mdoloris Medical Systems (software version 1.1) was used. ECG for ANI computation was obtained by two electrodes placed on the patient's chest. A PC ran a real time application developed in Matlab for the data acquisition. Information from the ANI monitor (ANI_m and ANI_i) was recorded automatically at a sample time of 5 seconds in the PC via a USB port. Two anesthesiologists took part in each intervention. Anesthesiologist 1 was in charge of the drug supply task. Anesthesiologist 2 oversaw the acquisition process and registered the variations of HR, BP and remifentanil changes in the Matlab application every five minutes as recommended in [27]. A detailed scheme of the collecting system developed in the operating theatre is shown in Figure 1.

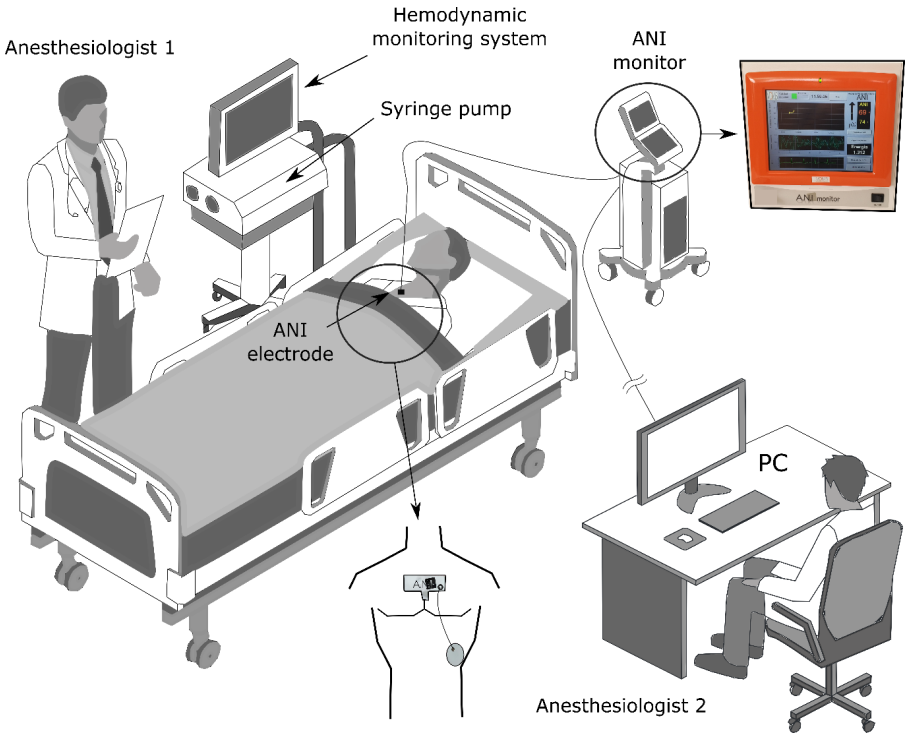

Figure 1. Scheme of the data acquisition process during the surgeries.

The main key of this study lies in the information displayed by the ANI monitor was not available for anesthesiologist 1 to avoid biasing their decisions. Apart from the changes in remifentanil, anesthesiologist 2 also wrote down the occurrence of relevant clinical events such as surgical stimuli or the titration of additional drugs. As clinicians were not familiar with the program, not only a PC, but also a data collection notebook was used for data recording of ANI, HR, BP every five minutes as well as the description of the main clinical events.

2.3. Data preprocessing

Before applying the machine learning algorithms, the dataset recorded was preprocessed according to the following steps:

1. *Identification of the goal information*. This study aimed to analyze those remifentanil changes that were based on the hemodynamic response of patients. As a matter of fact, changes due to the anticipation to surgical stimuli warned by the surgeon should not be taken into account for the analysis. According to the timeline presented in Figure 2, only changes between T_5 and T_6 were considered.

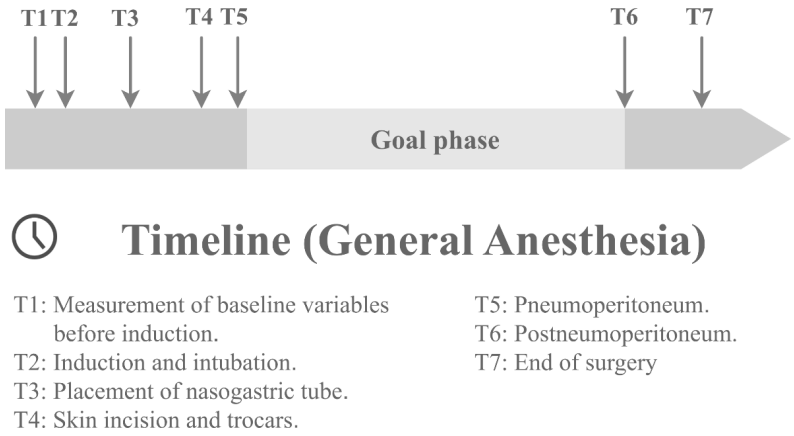

Figure 2. Timeline of the general anesthetic process in patients enrolled in this study.

2. *Validation of hemodynamic data*. To check the hemodynamic data, both anesthesiologists involved in the data collection process inspected the data recorded in the notebook after each surgery. According to the criteria of the experts, if an abnormal record of HR or BP was detected, that part of the intervention would be discarded for the analysis. Then, the information recorded in the computer was compared with the data collection notebook. In case of any divergence, notebook data prevailed against PC.
3. *Validation of ANI data*. The presence of some artifacts during the intervention worsened the quality of the signal. In those cases in which the monitor was not capable of processing the information from the sensor, it displayed a zero value for both ANI_i and ANI_m. It was observed that these situations remained for less than 2 minutes during the goal phase. Considering the dynamics of the signal, a linear interpolation was applied to reconstruct the index during this time frame. New values

at instant *k*, $k = \{0, T, 2T, \ldots, T_{error}\}$, were approximated using the values of the line that joined the two points immediately anterior (ANI_0) and posterior (ANI_{end}) to the failure during the time the error persisted (T_{error}) at each sample time T = 5s as:

$$ANI_k = ANI_0 + \frac{ANI_{end} - ANI_0}{T_{error}} \cdot k$$

4. *Matching the information from both sources.* In case of any complication during the surgery, the anesthesiologist 2 helped the anesthesiologist 1 with the anesthetic process except for the analgesic titration. Under this condition, and trying to avoid missing data, it was specified that the hemodynamic data would be only registered in the notebook. As a result, this information had to be included afterwards in the digital record for the analysis. The main problem lied in the divergences on the timestamp. Unlike the timestamp in the program, expressed as the time spent since the beginning of the surgery (expressed in seconds), the anesthesiologist linked each manual record with the time of day (expressed as HH:MM). To deal with this issue, a protocol for merging the information was designed. As the ANI values were automatically captured every 5 seconds in the PC and, given the fact that the anesthesiologist 2 also wrote down the ANI values every 5 minutes by hand, it was possible to match this information to synchronize both sources. Note that the same ANI_i and ANI_m tuples could have happened more than once along the surgery. To face this problem, different tentative times in the PC format were first assigned to each event recorded in the notebook. To do that, the timestamp of the "Incision" event was considered as the reference as this event was always recorded in both sources. Finally, to assign each manual record with the appropriate record in the PC, the Euclidean distance including ANI_i, ANI_m and time from both sources was computed. Those manual and PC values that resulted in the minimum Euclidean distance were linked for the analysis.
5. *Labelling the dataset*. After the evaluation of the hemodynamic state of the patient every five minutes, the anesthesiologist must have increased, decreased or kept the dose of remifentanil to ensure an appropriate analgesic state. A variation in the remifentanil infusion rate evidences an inadequate level of analgesia. According to

the main objective of this study, only those records associated with changes of the drug were considered for training the classifiers. Therefore, qualitative variables were defined as "Increment of drug" or "Decrement of drug" for these situations.

6. *Creating the csv file*. Each change of dose was kept as a different record. They included information about the evolution of HR, BP, ANI_i, ANI_m and remifentanil dose during the 10 minutes before a change. All the records were saved in a csv file to extract the information according to the input feature proposal.

2.4. Machine learning approach

According to the main objective of this study, different machine learning algorithms were trained to analyze whether including the Analgesia Nociception Index could outperform the decision making process only based on hemodynamic variables. Initially, an automated training was carried out to search the best classification model type among all the methods included in the Classification Learner toolbox provided by MATLAB2017a. Those methods corresponded to Decision Trees, Discriminant Analysis, Logistic Regression, Support Vector Machines, Nearest Neighbor Classifiers and Ensemble Classifiers. Different parameters were tested for each method as presented in [28]. After a preliminary analysis of the results (see Appendix), the four methods that performed best were proposed in order to carry out a more exhaustive analysis:

1. K-Nearest Neighbors (KNN) [29]: number of neighbors was set to 1 and the Euclidean distance was used.
2. Decision Tree (DT) [30]: Maximum number of splits was set to 4 and the GDI (Gini Diversity Index) was used as the split criterion.
3. Linear Discriminant Analysis (LDA) [31]: a linear discriminator with a Gamma parameter set to 0 was used.
4. Support-Vector Machine (SVM) [32]: a linear kernel function with a box constraint set to 1 and a kernel scale automatically selected was used.

First, the aim was to study the capability of the different outcoming models to predict the change of remifentanil in this problem. Specifically, this analysis focused on "Increment of

drug" and "Decrement of drug" decisions. To deal with overfitting, all these methods were subjected to a cross-validation procedure. In order to determine the suitability of the different methods, the following performance indicators were computed from the cross-validation process [33]: accuracy; specificity; precision; recall; Kappa index [34] and Area Under the Curve (AUC)

As only those changes of dose made in the goal phase of the surgery would be analyzed, a low number of records was expected. To face this issue, we proposed a 3-fold cross-validation repeated 100 times considering all the data obtained from the acquisition process. On the one hand, splitting the total amount of data in a low number of folds shows the prediction capability of each model. Higher performances would imply that a model is capable of learning the general behavior from a wide range of different situations, despite of the limitations in the number of training data. On the other hand, due to the low number of records, and trying to avoid the expected high variability in the results as a consequence of the fold configuration, the cross-validation process was repeated 100 times. Each record was randomly assigned to a fold at each iteration. The results were finally averaged to study the variability. In this sense, the more similar the results among iterations, the more robust the model in terms of the generalization capability. Once the best algorithm was identified, the performance focused on the input feature proposals was studied.

2.5. Feature proposal

To determine the impact of including the Analgesia Nociception Index in the decision making process, different feature vectors have been proposed to train the models. These variables include not only information about the evolution of ANI during the last five to ten minutes, but also about the traditional parameters considered in the standard clinical practice. First, the effect of including ANI derived information to predict a dose change is aimed. Particularly, it is important to determine if the performance of the machine learning algorithms purely based on hemodynamic information can be outperformed by including information from the ANI monitor. In the absence of any other clinical information, it will evidence the potential of using the ANI in the operating theatre to detect an inadequate level of analgesia compared with the hemodynamic information. In addition, as the ANI monitor has not been widely used

in the clinical practice, vague criteria to interpret the information displayed by the monitor has been defined. Considering the variations observed in the ANI signal during a five-minute period and, in order to perform a reliable comparison with the hemodynamic information recorded every five minutes, different features were extracted from the raw ANI_i and ANI_m that summarize the main characteristics during this time period. As a matter of fact, this study proposes four different feature vectors based on information captured from the ANI for training the different machine learning algorithms:

Feature vector proposal 1: Hemodynamic information. This feature proposal aims to represent the standard clinical practice, in which only hemodynamic information is considered. This includes information about the current values of the systolic pressure, diastolic pressure, heart rate and remifentanil infusion rate, as well as this information of the last 5 and 10 minutes before a change of drug dose.

Feature vector proposal 2: Minimum ANI information. This feature proposal includes not only the hemodynamic variables and remifentanil infusion rate as presented in the proposal 1, but also the information of the ANI_m averaged in the last 5 minutes as well as minimum ANI_i and ANI_m values registered during the last 5 minutes and 10 minutes before a change of remifentanil dose. As ANI_m has been presented as an indicator of the general analgesic state of the patient, this proposal aims to find possible correlations between the average of ANI_m and the change performed by the clinician. Furthermore, including minimum values reached by the ANI would make it easier to identify patterns related to an inadequate analgesia level, together with the evaluation of the monitor capability to predict hemodynamic events as presented in previous works.

Feature vector proposal 3: Maximum ANI information. Unlike feature proposal 2, maximum values of ANI will be evaluated instead. As a result, hemodynamic variables together with remifentanil infusion rate, the average of ANI_m in the last 5 minutes and maximum ANI_i and ANI_m values in the last 5 and 10 minutes will be included.

Feature vector proposal 4: ANI information. This input proposal is only based on the remifentanil infusion rate and on the ANI monitor. The main purpose is to evaluate whether

only including information about the ANI could outperform the prediction purely based on the hemodynamic information. To this end, maximum, minimum and mean values of ANI_i and ANI_m for different time span has been considered. Additionally, to determine the ANI_m trend during the last 5 minutes, the slope of the regression line that better fits the ANI_m evolution in the last five minutes has been computed. This feature adds information not only about the current trend, but also could be considered as a tentative prediction of the future evolution of ANI_m. The feature vector proposal together with each feature included is presented in Table 1.

Feature vector proposal	**Features**
1:Hemodynamic information	SP, SP_5, SP_{10} DP, DP_5 DP_{10} HR, HR_5, HR_{10} $Remi$, $Remi_5$, $Remi_{10}$
2: Minimum ANI	SP, SP_5, $SP_{10,}$ DP, DP_5 $DP_{10,}$ HR, HR_5, $HR_{10,}$ $Remi$, $Remi_5$, $Remi_{10,}$ $\widetilde{ANI}_{m5}$ $\underline{ANI}_{m5}$, $\underline{ANI}_{m10}$, $\underline{ANI}_{i5}$, $\underline{ANI}_{i10}$
3: Maximum ANI	SP, SP_5, $SP_{10,}$ DP, DP_5 $DP_{10,}$ HR, HR_5, $HR_{10,}$ $Remi$, $Remi_5$, $Remi_{10,}$ $\widetilde{ANI}_{m5}$ $\overline{ANI}_{m5}$, $\overline{ANI}_{m10}$, $\overline{ANI}_{i5}$, $\overline{ANI}_{i10}$
4: Only ANI	$Remi$, $Remi_5$, $Remi_{10,}$ $\underline{ANI}_{m5}$, $\underline{ANI}_{m10}$, $\underline{ANI}_{i5}$, $\overline{ANI}_{m5}$, $\overline{ANI}_{m10}$, $\overline{ANI}_{i5}$, $\widetilde{ANI}_{m5}$, $\widetilde{ANI}_{m10}$, $\widetilde{ANI}_{i5}$, ANI_{mtrend}

Table 1. Description of the feature vector proposal used for training the classifiers. SP_k: Systolic Pressure, DP_k: Diastolic Pressure, HR_k: Heart Rate, $Remi_k$: Remifentanil infusion rate, $ANI_{i,k}$: Instantaneous value of ANI as recorded from the monitor, $ANI_{m,k}$: Mean value of ANI as recorded from the monitor. Subscript *k* indicates the time span (in minutes) considered for the variable as described in the text. $\overline{ANI}, \underline{ANI}$ and $\widetilde{ANI}$ represents maximum, minimum and mean values respectively of the corresponding variable. ANI_{mtrend} is the trend of the ANI_m.

The same clinical dataset captured for the training phase will be used for this analysis. Finally, three different scenarios representing real situations during anesthesia according to the expert's criteria will be proposed for the evaluation of the classifier:

1. *Urgent changes*: Those changes that must be undoubtedly performed according to the clinical signs of the patient. An urgent change should be carried out when an (absolute) variation of the arterial systolic pressure > 25% occurs in the last five minutes.
2. *Non-urgent changes*: These records represent those changes that are not based on a strong variation in the hemodynamic activity. These changes could have been based

on external factors not recorded in the study such as movements, a compensation of a previous change, or even a prediction of a possible hemodynamic event in the next minutes regarding the recent hemodynamic evolution.

3. *Keep the current dose*: These records represent an absence of change motivated by an accurate analgesic state of the patient. During the data collection phase in this study the clinicians did not report any insight to motivate a no-change of dose decision. To deal with this issue, a conservative criterion to include only those situations in which a no-change of drug could be potentially justified by an appropriate analgesic state of the patient is defined:
    - Only those decisions that resulted from the update of the hemodynamic information every 5 minutes should be included.
    - A record in which the dose was kept should be included in the analysis only if the decision was made, at least, ten minutes after the last change of dose. The main objective is to minimize the impact of those clinical factors depending on pharmacological considerations. If so, it can be assumed that the decision of keeping the dose of drug is mainly due to an appropriate level of analgesia.
    - Only those records followed by no changes of dose during the next ten minutes are evaluated. Previous research claims that the ANI monitor is capable of anticipating the appearance of hemodynamic events in the next ten minutes. If no evidence of nociception is inferred in the next ten minutes and, consequently, no change of dose has been made, it can be assumed that the values displayed by the ANI monitor are compatible with an appropriate analgesic level.

As the trained classifier will be dichotomous, i.e. only increments or decrements can be predicted, the analysis of the posterior probability associated with each prediction is proposed for the evaluation of the classifier [35].

3. Results

17 subjects (4 males, 13 females, age: 59 ± 11.6 years, weight: 77.47 ± 14.79 kg, height: 164.94 ± 7.39 cm) were enrolled in the study. No abnormal situation was reported during the post-operative evaluation of analgesia in any of the 17 surgeries included in the study. A total of 58 changes of remifentanil infusion rate (34 increments vs. 24 decrements) were performed during the goal phase of the surgery. The mean number of dose changes per patient was 3.4 ± 2.4. An example of the clinical data recorded for this study during the surgeries is shown in Figure 3.

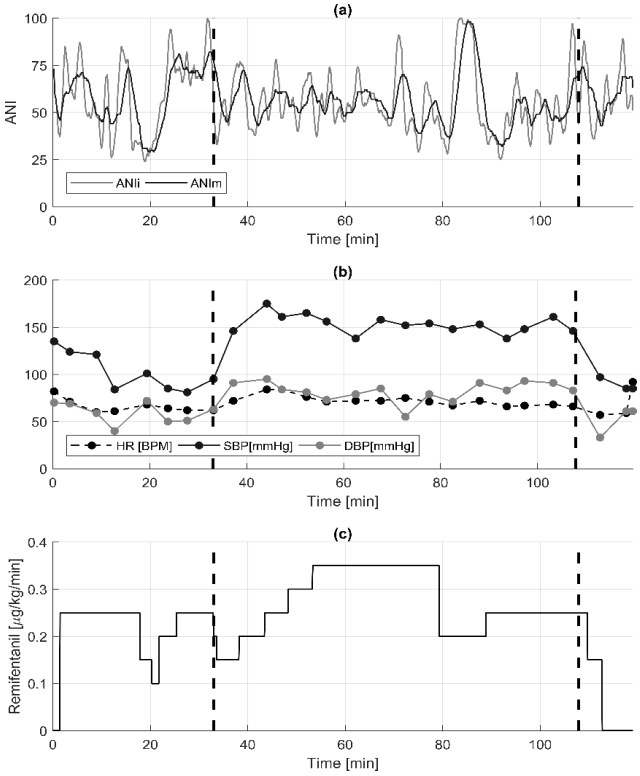

Figure 3. Evolution of the clinical variables recorded during the study: (a) represents the evolution of instantaneous ANI (ANI_i) and mean ANI (ANI_m). (b) corresponds to the evolution of the hemodynamic variables measured every 5 minutes. (c) shows the changes of the remifentanil infusion rate during the surgery. Dashed lines represent the beginning and end, respectively, of the target period considered for this study (T_5 and T_6 respectively).

Table 2 shows the performance of the different classifiers trained in this study after applying a 3-fold cross validation repeated one hundred times for each input proposal as described in section 2.4. Regardless of the input combination used for the training dataset, the best results were reached when training the Support Vector Machines. Specifically, considering the input proposal number 2, Kappa index and Area Under the Curve increased 0.24 and 0.12 respectively when applying SVM compared with the performance reached by LDA. Under the same conditions, a decrement of the Standard Deviation obtained from the one hundred iterations was also observed. In light of the results, we applied this model to perform further analysis of the data.

Figure 4 shows a graphical comparison of the performance reached by the SVM models depending on the input feature vectors. Given the fact that the predictor 1 represents the standard situation in which only the hemodynamic information has been considered, the performance of the other classifiers is compared to determine the impact of including ANI in the decision making process. A better performance was observed when training the predictor 2. Considering the accuracy as the capability of matching predictions with the real decisions, the model based on both hemodynamic information and minimum ANI index-derived features reached a score of 86.21% (83.62%-87.93%). This result outperformed the accuracy reached by the predictor number 1 of 82% (79.31%-84.48%), based only on hemodynamic information. Including only the ANI index information decreased the accuracy to 60% (56.90%-62.07%).

For the evaluation of the performance depending on each kind of decision, i.e. increments and decrements of remifentanil infusion rate, precision and recall as well as specificity were analyzed. On the one hand, precision and recall indexes can be regarded as measures to quantify the performance of the classifier when predicting increments of the drug. In this sense, classifier 2 was capable of predicting 91.18% (88.24%-91.18%) of the increments of drug correctly, compared to 88.24% (85.29%-91.18%), 85.29% (82.35%-88.24%) and 76.47% (70.59% - 79.41%) reached by classifiers 1, 3 and 4 respectively. Moreover, not only a higher median value, but also a narrower interquartile range reached by model 2 evidences the generalization capacity to predict increments of remifentanil regardless of the specific fold considered for the training. In addition, similar conclusions were reached when studying the precision score.

Method	Feature Vector	Accuracy	Specificity	Precision	Recall	Kappa	AUC
KNN	1	72.84± 4.33	61.71± 6.37	74.96± 3.44	80.71± 5.83	0.43± 0.089	0.71 ± 0.043
	2	64.45± 4.03	58.00± 6.20	70.00± 3.62	69.00± 4.53	0.27± 0.083	0.63± 0.042
	3	68.29± 4.30	61.33± 6.65	72.91± 3.75	73.21± 5.88	0.35± 0.087	0.67± 0.043
	4	55.09± 6.09	56.63± 10.63	64.10± 6.62	54.00± 6.19	0.10± 0.13	0.55± 0.065
DT	1	69.95± 5.78	70.42± 10.23	77.33± 6.46	69.62± 7.72	0.39± 0.12	0.73± 0.065
	2	68.52± 5.58	66.21± 10.97	75.04± 5.84	70.15± 8.78	0.36± 0.11	0.71± 0.07
	3	68.66± 5.84	68.54± 9.97	75.89± 6.14	68.74± 7.66	0.37± 0.12	0.71± 0.069
	4	54.91± 6.2	47.79± 9.43	61.82± 4.97	59.94± 10.63	0.11± 0.078	0.55± 0.069
LDA	1	78.09± 4.09	71.42± 7.11	80.54± 4.12	82.79± 3.97	0.55± 0.086	0.80± 0.038
	2	72.90± 5.29	67.29± 7.64	77± 4.61	76.85± 6.57	0.44± 0.11	0.76± 0.050
	3	72.02± 4.58	67.29± 6.79	76.64± 4.01	75.35± 6.47	0.43± 0.091	0.75± 0.043
	4	52.88± 5.81	42.38± 8.38	59.66± 4.75	60.29± 8.04	0.027± 0.12	0.53± 0.06
SVM	1	81.14± 3.87	73.08± 6.22	82.14± 3.57	86.82± 4.29	0.61± 0.081	0.87± 0.025
	2	84.45± 3.58	79.13± 6.50	85.82± 3.85	88.21± 3.53	0.68± 0.075	0.88± 0.023
	3	80.78± 4.67	72.33± 8.17	81.80± 4.64	86.74± 4.61	0.60± 0.99	0.87± 0.032
	4	59.91± 4.65	39.00± 7.69	63.46± 3.46	74.68± 5.9	0.14± 0.99	0.60± 0.046

Table 2. Classifier performance indices expressed as Mean ± SD for different machine learning algorithms and features. KNN: K-Nearest Neighbors, DT: Decision Tree, LDA: Linear Discriminant Analysis, SVM: Support Vector Machine. Feature Vector as enumerated in Table 1.

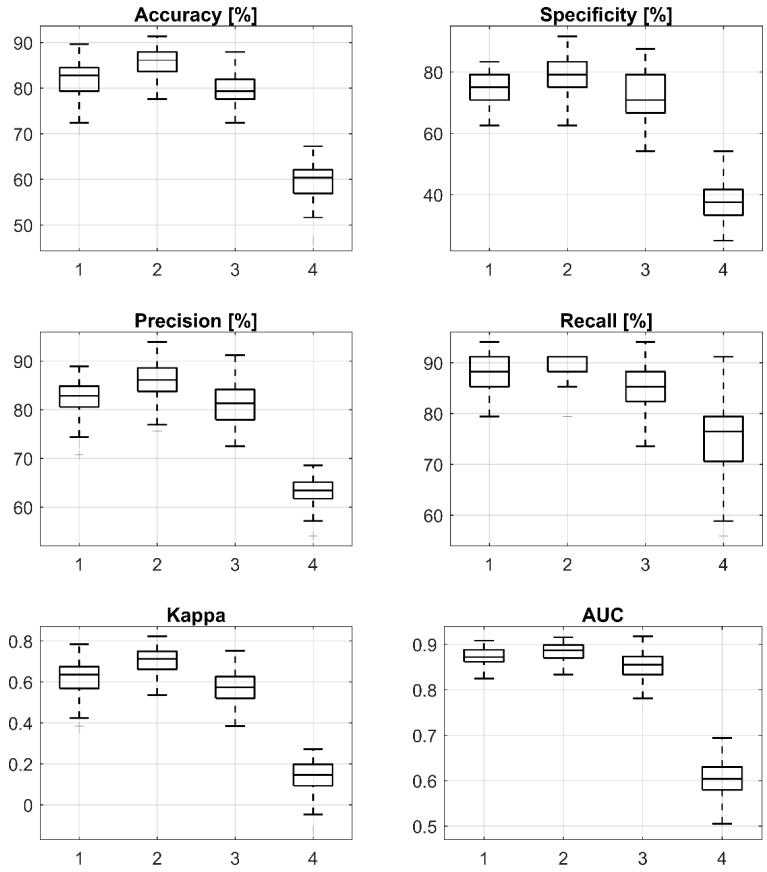

Figure 4. Boxplots representing the performance of the SVM models for the different input proposals.

On the other hand, the capability of predicting the decrements of the infusion rate was also studied. Specificity values of 75% (70.83%-79.17%), 79.17% (75%-83.33%), 70.83% (66.67-79.17%) and 37.5% (33.33%-41.67%) were respectively reached by the different predictors. In this case, introducing information about the minimum values of ANI index also allowed improving the decision making process focused on decrements of the drug. Despite of the acceptable results reached by some of the classifiers, it is important to note that lower values are reached when comparing specificity with recall scores. It could be due to the training dataset included more samples involving increments of drug rather than decrements. Notwithstanding

the fact, regarding the clinical scenario described in this analysis, to predict the increments of drug accurately is a critical decision in order to avoid chronic pain and short times of recovery after the surgery. Considering the low range of remifentanil infusion rate proposed in the clinical protocol, not decreasing the analgesic dose could rarely provoke a damage for patients. In fact, clinicians tend to overdose analgesic drug to prevent painful situations for patients in the recovery phase.

Furthermore, the general behavior of the classifiers was tested through AUC and Kappa index. Unlike the previous analysis, AUC scores for predictors 1 and 2 slightly differs, 0.87 (0.86-0.89) vs. 0.89 (0.87-0.90) respectively. Conversely, Kappa index firmly showed that better results were reached when considering not only hemodynamic evolution, but also minimum ANI information during the last 10 minutes. In addition, both AUC and Kappa index evidenced a poor performance when the remifentanil changes only depended on the information derived from the ANI monitor.

In light of the above, combining features involving both hemodynamic evolution and minimum ANI values during the 10 minutes before a change of dose outperformed those decisions made by the anesthesiologist only based on hemodynamic information. Moreover, introducing information about maximum ANI was not enough for improving the decisions based on traditional clinical criteria. It is important to highlight that using only ANI as a guiding variable for remifentanil dosage during anesthesia worsened the decision-making process.

Finally, the capability of model 2 for predicting each individual change included in the dataset was analyzed. For this purpose, the results of the predictions after the cross-validation process performed in each iteration was computed. Success rate per change considering the 100 iterations is depicted in Figure 5. It showed that 76% of changes were predicted according to the clinician's criteria achieving a success rate within 90%-100%. Specifically, 55% of the predictions were always right regardless of the iteration. Despite of these promising results, there were at least 7 situations with a success rate under 60%. To deepen in the limitations of this proposal, these situations were analyzed.

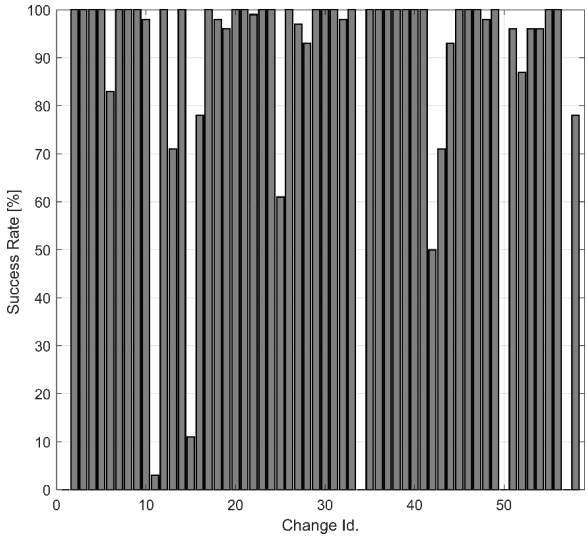

Figure 5. Success Rate expressed as the % of times that the SVM predictions matched each decision of the clinician for the features proposal number 2.

On the one hand, changes number 11, 34, 42 and 57 were characterized by a similar trend in terms of hemodynamic variables and ANI evolution that resulted in discrepancies when comparing the predictor response with the clinician's decisions. Small changes in heart rate as well as in blood pressure were observed during the previous ten minutes. These slight variations in the hemodynamic variables could evidence a questionable decision. In fact, some of these changes might have been based on the previous remifentanil infusion rate as it was set in the limits of drug allowed in the clinical protocol (0.05µg/kg/min and 0.4µg/kg/min). As a matter of fact, a boundary value of remifentanil could result in a slanted decision when small hemodynamic variations were observed. In addition, these four cases were related to ANI values that reported an unacceptable level of analgesia according to the instructions of the monitor. In order to check the effectiveness of the decision made by the clinician in these four decisions, changes in the remifentanil infusion rate performed in the next ten minutes after the change were also analyzed. It was observed that the clinician had to amend the decision due to the presence of post-risky hemodynamic events registered. In conclusion, despite of existing a

divergence with the decision of the clinician, considering both hemodynamic and ANI information could have avoided the hemodynamic reactivity in patients.

On the other hand, change number 50 seems to derive from an error when acquiring data during the intervention. Probably, there was a delay between the real change of dose and the instant in which the second anesthesiologist recorded the change in the computer. As a consequence, the variations in both hemodynamic variables and ANI evolution considered for the training process could have been affected by the pharmacological effect of the real change of dose. It is important to highlight that it was a punctual situation due to the manual acquisition of remifentanil that did not distort the procedure defined for the data collection. Finally, changes number 1 and 15 did not follow any of the patterns analyzed so far. Both cases consisted of variations in hemodynamic variables directly opposed to the information displayed by the ANI index. In this sense, these changes might have been based on additional information not recorded in the program, such as a possible anticipation of a surgical stimulus warned by the surgeon. Likewise, it is important to point out that heart rate and blood pressure are not exclusive measures of the sympathetic-parasympathetic balance of the nervous system. As a result, other physiological events beyond analgesia could have provoked these hemodynamic variations. Consequently, new studies should be carried out to analyze the possible uncertainties that may affect the process in order to deal with them.

3.1. Analysis of the two-class classifier in different clinical situations

According to the criteria defined in subsection 2.6, 26 urgent cases, 32 non-urgent cases and 16 situations in which the dose was kept were identified throughout the 17 interventions. The performance of the two-class classifier was evaluated in the three proposed scenarios. The posterior probability of the predicted class has been computed for the analysis. Consequently, probabilities ranging from 0.5-1 were obtained. Figure 6 summarizes main results of the classification when an urgent or non-urgent change of remifentanil was needed. For the study of those situations where the remifentanil dose was kept and, given the fact that the trained classifier was dichotomous, Figure 7 merely shows the posterior probability distribution for each prediction.

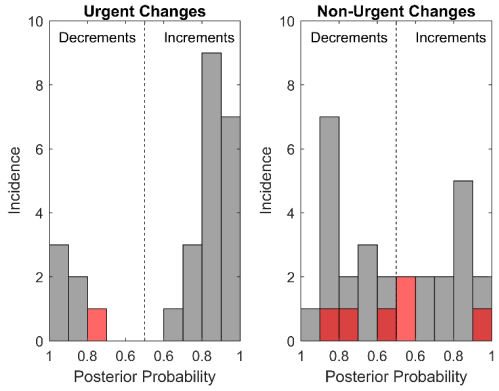

Figure 6. Posterior probability distribution when predicting urgent/non-urgent increments and decrements of remifentanil. Red bars represent misclassification.

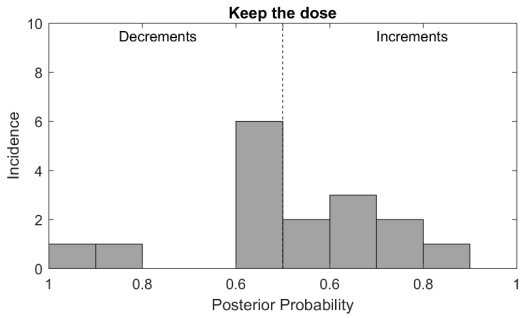

Figure 7. Posterior probability distribution when classifying those cases in which the dose was kept.

It was observed that 96% of the urgent cases were accurately predicted by the SVM classifier. In addition, 81% of those cases in which an urgent change was needed were correctly classified with a posterior probability greater than 0.8. The 84% of the non-urgent changes were correctly classified. Particularly, 72% of the non-urgent labelled changes resulted in an accurate classification with a posterior probability greater than 0.65. In those situations in which the dose was not changed, 62% of the records were predicted as increments or decrements of drug with a posterior probability lower than 0.65. Thus, the current classifier was not confident enough to decide whether these cases corresponded to an increment or a decrement of the remifentanil

infusion rate. This evidences that these records included information that was not compatible with the patterns learned for the classification in any of the two classes. It was also observed that those predictions that resulted in a posterior probability greater than 0.65 matches the change performed by the clinician in the next 10-15 minutes

Considering the previous results of the classifier in the different scenarios, we have studied the suitability of the current classifier to predict the three possible actions during anesthesia: increment, decrement or no change of dose. The synthesis of the three-class classifier was based on the posterior probability analysis. To this end, the original classifier would predict a "Keep the dose" action if the resulting posterior probability was lower than 0.65. The proposed three-class classifier reached in an accuracy of 77% when predicting the different actions. The confusion matrix that summarizes the general performance is shown in Table 3. These results may evidence that the original classifier is not only capable of distinguishing patterns belonging to critical cases (increments or decrements of drug) but also detects information that does not belong to any of these two categories that could be related to no-change of drug.

		Real Action		
		Increment	Decrement	Keep
Predicted Action	Increment	29	1	4
	Decrement	3	18	2
	Keep	2	5	10

Table 3. Confusion matrix of the three-class classifier.

4. Discussion

In this paper, we have studied the suitability of the Analgesia Nociception Index to provide valuable information to guide the analgesic drug titration during general anesthesia. Specifically, we have proposed a new scheme based on machine learning classifiers to study the effect of introducing the ANI monitor to replicate the decisions of the experts in critical situations where a modification of dose is required.

This study was based on the clinical data captured from 17 patients undergoing cholecystectomy surgeries. The results of this research evidences that considering the minimum

values of ANI during the last 10 minutes let outperform the decisions made regarding the traditional criteria considering only the hemodynamic information. An accuracy of 86.21% (83.62%-87.93%) was reached when using a SVM. Similar performances have been reached when applying machine learning methods in drug titration. In proton therapy, an accuracy ranging from 0.75 to 0.88 was reached when applying a leave-one-out study to predict the discrepancies between planned and real dose [36]. In cancer drug therapies, the prediction score for optimal drug dose reached a 0.8 of accuracy [37]. In addition, a median kappa index of 0.71 turns our classifier into a good tool for prediction [38]. It was observed that this monitor does not only help in the decision making process, but also is capable of predicting and avoiding errors in the drug titration process.

To complete this study, we have also analyzed the behavior of the classifier for the predictions of different situations observed in the clinical practice. The results pointed out that urgent changes of remifentanil were mostly accurately predicted with a high confidence level. In addition, the two-class classifier presented a low confidence level when evaluating those cases in which the dose of drug was kept. This fact may evidence that the feature proposal based on hemodynamic information together with minimum ANI values provides enough information to distinguish, not only between critical situations where an increment or decrement of drug is needed, but also to detect those situations where an appropriate level of analgesia is observed.

The main difference with respect to previous published works lies in the methodology used. Specifically, the proposed analysis based on machine learning together with a non-invasive scheme for the analysis of the monitor constitutes one of the major novelties of this work. Most of the previous research has been based on the validation of the ANI monitor in the clinical stage. Main trend has been based on establishing a correlation between values of ANI recorded during the surgery and post-operative pain reported by the patients through VAS scores. In [18], an association between acute postoperative pain and ANI scores was reported with very high negative predicted values of higher ANI scores (>57) for determining acute pain. However, several posterior studies reported no relation between both variables [39, 40]. One important weakness of these previous studies lies in the presence of subjectivity when including the patient evaluation of the postoperative pain since the perception of pain differs from persons [41]. For the evaluation of the ANI monitor in this study, subjectivity of patients has not affected

the results. Thus, the suitability of the monitor has been evaluated through its capability to report valuable information in order to replicate the actions of the anesthesiologist during the surgery. Furthermore, unlike previous studies, our strategy is not based on an invasive scheme, preventing harmful situations for the patient derived from the application of painful stimuli.

Although this study constitutes a new point of view for the evaluation of ANI, some of the conclusions reached can be compared with previous published works. Some of the results analyzed in our study have evidenced the capability of anticipating hemodynamic events during the surgery. Particularly, it was observed that the evolution of the ANI index may warn the appearance of a hemodynamic event in the next 10-15 minutes despite of the absence of change in heart rate or blood pressure. In [42], sensitivity and specificity (88% and 83%) evidenced the predictive capability of ANI to anticipate hemodynamic changes in the next 5 minutes. Other studies, however, have detected a low probability of ANI to detect hemodynamic reaction [43].

This study presents some limitations that should be taken into account. First, only 58 records involving changes of remifentanil were recorded throughout the 17 surgeries. This may seem a low number of records for the application of machine learning techniques. However, the analysis of the performance presented in Section 3 considering not only mean values, but also the deviations resulting from the 100 iteration of a 3 cross-validation overcomes this difficulty. From the clinical perspective, 58 cases may have not described all the possible situations observed in the clinical practice in which a change of dose is required. To deal with this issue, future research should be conducted to include a higher number of records. Notwithstanding that fact, note that the current SVM classifier was capable of predicting accurately urgent changes of doses with a high confidence interval. Consequently, new urgent cases based on hemodynamic information may be also predicted by the classifier. In addition, the performance of the monitor in other kind of surgeries should be also analyzed. Note that this study has been only focused on those decisions made according to the analgesic state of the patient rather than on other factors depending on the kind of intervention. To this end, a specific phase of the surgery was analyzed. Consequently, low variations of the results are expected when trying the classifier in new kind of surgeries. Further studies should be conducted to this end. Finally, collecting new cases will be also helpful to study possible slight variations introduced in the decisions making process towards a more personalized titration. These variations are widely

known as interpatient and intrapatient variability. New studies should include more cases to detect relevant events in the ANI monitor that may be correlated with this factor. Additionally, increasing the number of records will also make possible the proposal of a new analysis based on a time series forecasting problem including information of the ANI for remifentanil prediction.

It is important to highlight that the main objective of this research was not the proposal of an automatic system to supply drug during anesthesia, but a new approach to study the capability of the ANI monitor to replicate decisions of the anesthesiologist when a bad level of analgesia is detected. Thus, this research constitutes a new step towards the development of a closed-loop solution for remifentanil titration. The main aim will be the design of an application capable of guiding the decision making process in the operating room towards an integral automation of the anesthetic process.

5. Conclusion

The main goal of this research was the analysis of the information provided by the Analgesia Nociception Index as a valuable tool to replicate the actions of the anesthesiologist in remifentanil analgesia. A non-invasive clinical scheme together with the use of machine learning algorithms for the analysis are presented. The results evidenced that (i) including data of the minimum ANI values recorded during the last 10 minutes outperforms those decisions only based on hemodynamic information; (ii) ANI may be capable of anticipating the need of a change of dose before the appearance of a hemodynamic event and (iii) the resulting SVM performs accurate predictions under different situations commonly observed in the clinical practice, particularly when an urgent change of dose must be made. As far as we are concerned, this is the first study in which the actions of the clinicians based on hemodynamic information has been objectively correlated with the information displayed by the ANI monitor during anesthesia. Despite of more research is needed to test the suitability of ANI, including a higher number of patients and types of surgeries, the promising results will motivate the development of an intelligent structure based on the information provided by the ANI monitor for a closed-loop control of remifentanil analgesia.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Appendix

This appendix presents the results of the preliminary study performed to determine the machine learning algorithms and parametrization finally included in this study. To this end, all the methods included in the Classification Learner toolbox provided by MATLAB2017a were tested. Parametrization used for each method was presented in [28]. For the evaluation, a 3-fold cross-validation was repeated 5 times per each classifier type. The resulting mean accuracy of the 5 tests is presented in Table A.1. Finally, the 4 classifiers with the highest performance were proposed for the study. Only one classifier per group was considered for the study.

Classifier Group	Classifier Type	Feature vectors				Mean
		1	2	3	4	
Decision Trees	Complex Tree	70.0	67.9	69.0	53.1	65.0
	Medium Tree	70.0	67.9	69.0	53.1	65.0
	Simple Tree	70.7	68.6	69.7	53.1	65.5
Discriminant Analysis	Linear Discriminant	77.6	72.1	67.6	52.1	67.3
	Quadratic Discriminant	62.7	0.0	0.0	47.6	27.6
Logistic Regression	Logistic Regression	66.7	64.6	62.1	53.8	61.8
Support Vector Machines	Linear SVM	79.0	83.5	77.6	55.8	74.0
	Quadratic SVM	74.8	75.5	79.3	45.5	68.8
	Cubic SVM	74.8	70.3	75.8	47.3	67.1
	Fine Gaussian SVM	69.3	58.6	58.6	57.2	60.9
	Medium Gaussian SVM	77.9	76.2	76.6	54.5	71.3
	Coarse Gaussian SVM	60.3	59.3	58.6	58.9	59.3
Nearest Neighbor	Fine KNN	73.5	63.8	64.2	49.0	62.6
	Medium KNN	65.4	63.9	65.6	39.5	58.6
	Coarse KNN	51.0	58.6	58.6	51.0	54.8
	Cosine KNN	64.2	65.4	63.3	49.2	60.5
	Cubic KNN	64.8	63.6	66.6	48.0	60.8
	Weighted KNN	64.6	64.2	65.4	45.0	59.8
Ensemble Classifiers	Boosted Trees	58.6	58.6	58.6	58.6	58.6
	Bagged Trees	63.4	63.8	61.4	55.1	60.9
	Subspace Discriminant	67.2	65.8	65.2	47.8	61.5
	Subspace KNN	64.3	61.7	60.5	52.1	59.6
	RUSBoosted Trees	61.2	55.9	58.8	47.2	55.8

Table A.1. Accuracy obtained for the preliminary study when performing a 3-fold cross-validation repeated 5 times. Feature vectors as presented in subsection 2.5. Classifiers finally selected for the analysis are highlighted.

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Appendix A – III. Adaptive drug interaction model to predict depth of anesthesia in the operating room

This Appendix presents the third paper included in the compendium of publications. This paper proposes a new methodology for modeling the depth of hypnosis during anesthesia. This proposal relies on an adaptive model capable of dealing simultaneously with the drug interactions, the variabilities in the clinical response of the patients, and the variable time delay introduced by the BIS monitor.

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Adaptive drug interaction model to predict depth of anesthesia in the operating room

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ABSTRACT

The availability of accurate models for predicting the drug effect in patients undergoing general anesthesia is an important factor in producing a personalized drug infusion. These models should consider different clinical factors to provide realistic predictions. This paper proposes a new methodology for modeling the depth of hypnosis (DOH) during anesthesia. The model, which is based on a pharmacokinetic–pharmacodynamic structure, explicitly takes into account the interaction between the hypnotic and opioid drugs delivered during surgery. Patients undergoing general surgery with intravenous propofol–remifentanil anesthesia were considered. The bispectral index (BIS) was used for monitoring the DOH. In contrast with previous research, the uniqueness of this study lies in the proposal of an adaptive model to deal simultaneously with the variabilities in the clinical response of the patients, the drug interactions, and the variable time delay introduced by the BIS monitor. The proposed method was validated using data from 17 patients undergoing general anesthesia. Successful results were obtained for predicting the evolution of BIS during the induction and maintenance phases of propofol–remifentanil anesthesia. Specifically, the convenience of an adaptive model that included all the factors likely to affect the anesthetic process was demonstrated. The proposed methodology can be used for the development of new models to be employed in model predictive control strategies for closed-loop anesthesia.

1. Introduction

One of the main trends in medicine is personalized medicine. This field includes tailoring an individualized drug titration according to the characteristics of the patient. The successful administration of drugs depends on extensive knowledge of the clinical process. The expertise of clinicians is often based on mathematical models capable of representing the physiological process to predict the effects of a drug on the patient. However, the synthesis of theoretical models is sometimes difficult because of the complexity of physiological systems.

An accurate drug dosage may result in optimal therapies and enhance the safety of patients. In anesthesia, an accurate drug dosage has been correlated with shorter recovery times and fewer side-effects in patients [1]. The anesthetic process is focused on the control of three main variables: hypnosis, analgesia, and muscle relaxation. Thus, delivering a proper dose of the different drugs in the process is critical, not only to ensure the optimal conditions for the intervention but also to avoid unwanted dangerous outcomes.

In clinical practice, total intravenous anesthesia (TIVA) is mainly used for drug delivery. For the control of hypnosis, manual infusion of propofol (the hypnotic agent) is one of the most widely used techniques. Here, the depth of hypnosis (DOH) must be continuously measured to assess the hypnotic level of the patient. Among the different monitors available, the bispectral index (BIS) is one of the preferred options among clinicians [2]. It is based on a noninvasive method to quantify the level of hypnosis through electroencephalogram (EEG) analysis, providing a dimensionless number ranging from 0

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Abstract

The availability of accurate models for predicting the drug effect in patients undergoing general anesthesia is an important factor in producing a personalized drug infusion. These models should consider different clinical factors to provide realistic predictions. This paper proposes a new methodology for modeling the depth of hypnosis (DOH) during anesthesia. The model, which is based on a pharmacokinetic–pharmacodynamic structure, explicitly takes into account the interaction between the hypnotic and opioid drugs delivered during surgery. Patients undergoing general surgery with intravenous propofol–remifentanil anesthesia were considered. The bispectral index (BIS) was used for monitoring the DOH. In contrast with previous research, the uniqueness of this study lies in the proposal of an adaptive model to deal simultaneously with the variabilities in the clinical response of the patients, the drug interactions, and the variable time delay introduced by the BIS monitor. The proposed method was validated using data from 17 patients undergoing general anesthesia. Successful results were obtained for predicting the evolution of BIS during the induction and maintenance phases of propofol–remifentanil anesthesia. Specifically, the convenience of an adaptive model that included all the factors likely to affect the anesthetic process was demonstrated. The proposed methodology can be used for the development of new models to be employed in model predictive control strategies for closed-loop anesthesia.

Keywords: bispectral index; depth of anesthesia; drug interactions; interpatient variability; intrapatient variability; PK–PD model.

1. Introduction

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In clinical practice, total intravenous anesthesia (TIVA) is mainly used for drug delivery. For the control of hypnosis, manual infusion of propofol (the hypnotic agent) is one of the most widely used techniques. Here, the depth of hypnosis (DOH) must be continuously measured to assess the hypnotic level of the patient. Among the different monitors available, the bispectral index (BIS) is one of the preferred options among clinicians [2]. It is based on a noninvasive method to quantify the level of hypnosis through electroencephalogram (EEG) analysis, providing a dimensionless number ranging from 0 (absence of brain activity) to 100 (fully conscious patient). BIS values between 40 and 60 are recommended for general anesthesia [3].

The application of closed-loop strategies based on the BIS monitor for the control of hypnosis has emerged as a field of interest for both clinicians and engineers. Different strategies have been clinically tested and have outperformed manual administration [4–6]. The success of most of the strategies lies in the availability of an accurate patient model for the controller design. This has been a critical concern for the development of model predictive controllers (MPC) [7]. Robust controllers have been also proposed to deal with uncertainty in model identification [8, 9]. Other control strategies based on more individualized approaches have been proposed [10]. The same considerations are important in target-controlled infusion. This technique is based on an open-loop strategy in which the syringe pump infuses propofol according to a clinical model to ensure the appropriate drug concentration [11]. However, this technique may result in problems if there are large discrepancies between the patient response and the mean-population models.

Consequently, the availability of clinical models presents a significant challenge for the improvement of the current model-based methodologies. In the field of anesthesia, various models have been proposed for propofol-based anesthesia. The main approaches have been

based on clinical pharmacological models [12, 13]. These studies mostly use data collected from large heterogeneous groups of patients during surgery. Recently, new techniques based on artificial intelligence have allowed the development of new models for the prediction of anesthesia [14–16]. Regardless of the methodology, different studies have concluded that the main problem for the model identification arises from the variabilities introduced by the patients. Large variations in the responses of patients with respect to covariate factors, such as the age, gender, and weight of the patients, have been observed [17]. In addition to this interpatient variability, significant differences in the responses of the same patient throughout the different phases of the anesthetic process have been observed [18].

Importantly, the simultaneous titration of different drugs may result in drug interactions, which should be included in the model. Additive interactions have been observed between propofol and remifentanil (analgesic drug) while controlling the hypnotic level during general anesthesia [19]. Most of the proposed models that describe the anesthetic process are single-input single-output models. The roadmap to personalized medicine implies the extension of these models to multiple-input single-output or multiple-input multiple-output models. Recent studies have considered the effect of the simultaneous infusion of different drugs for anesthesia regulation [20]. In addition to these clinical considerations, other factors should be considered while applying a closed-loop strategy. In particular, using the BIS monitor for assessing hypnosis introduces variable time delays in BIS-guided anesthesia. This degrades the performance of the strategy and may result in unstable systems when closed-loop schemes are used [21].

In previous studies in this field, researchers proposed partial solutions including some of the aforementioned factors [22]. However, the development of a model dealing with the different factors likely to affect the anesthetic process remains a challenge. The main objective of the present study was to develop an identification algorithm based on optimization techniques to model the hypnotic level of patients in propofol–remifentanil anesthesia. The final structure is based on a parametric pharmacokinetic–pharmacodynamic (PK–PD) model that is capable of dealing with (i) interpatient and intrapatient variabilities (through an iterative identification algorithm to adapt the model parameters), (ii) propofol–remifentanil interactions (through a structure that models the additive effect of both drugs), and (iii) variable time delays introduced

by the BIS monitor (this parameter is included in the identification process). To the best of our knowledge, this is the first strategy in which all the potential influencing factors are included in a model simultaneously. The proposed approach has applications in both clinical and engineering fields. This new identification algorithm can be implemented in MPC controllers to predict the future BIS evolution, as it is capable of minimizing deviations from the target during surgery [23].

The remainder of this paper is organized as follows. First, we introduce the basis for PK–PD modelling of hypnosis in propofol anesthesia. Then, the mathematical structure for dealing with additive drug interactions is presented. Potential problems with patient variabilities, as well as the source of delay introduced by the BIS monitor, are described. Next, we present the proposed algorithm for the model identification. In Section 4, the data-acquisition process is described. In Section 5, the model is validated by comparing its predictions with real data. Finally, the results are discussed, and the main conclusions are presented.

2. Model description

In pharmacology, compartmental models have been used as dynamic representations capable of capturing the exchange of drugs between coupled compartments in the human body. They consist of a representation of the human body as a finite number of compartments, each connected with a flow of substance from one compartment to another. Each compartment unifies the different tissues, considering their pharmacokinetic characteristics; thus, this structure is a theoretical simplification of the human body [24]. In the field of anesthesia, these models have been widely used to describe both the pharmacokinetics (PK) and the pharmacodynamics (PD) of drugs in the body. The main objective of this section is to analyze the available PK–PD models in anesthesia. The clinical effect of propofol–remifentanil interactions on BIS as well as the relevance of including the interpatient and intrapatient variability in the model are discussed. Finally, the importance of considering the time delay of the BIS signal is analyzed.

2.1. PK–PD models

Pharmacokinetic models quantitatively describe the effects of the drug dose in the plasmatic concentration of the different compartments that belong to the compartmental model. These effects depend on the absorption and distribution rates, metabolism, and drug elimination. Thus, a PK model is a mathematical expression that can predict the concentration evolution of a specific drug in a certain compartment. The effect concentration of the drug on a clinical variable, *Ec*, can be virtually represented by an additional virtual effect compartment. This effect compartment is assumed to have a negligible volume so that no mass transfer occurs from the PK model. The general structure of the PK model typically used in anesthesia is presented in Figure 1. The central compartment represents plasma and tissues in which the distribution of the drug is practically instantaneous. The fast and slow compartments are the peripheral compartments, including organs that are less well-perfused [25].

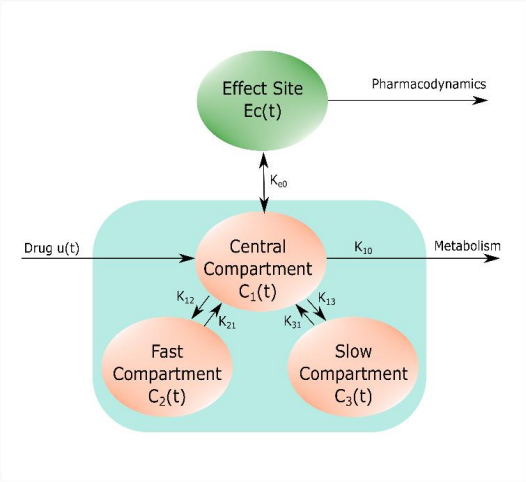

Figure 1. Structure of the PK model based on three compartments and an effect site compartment.

The drug mass variation in a specific compartment *i*, i.e., $\dot{m}_i$, can be expressed as follows:

$$\dot{m}_i = \sum_{j=1}^{n} k_{ji} m_j - \sum_{j=0}^{n} k_{ij} m_i + u_i. \quad (1)$$

Here, n represents the number of compartments; k_{ji} represents the increments of the drug mass characterized by the mass transfer rate from compartment j; k_{ij} represents the decrements of the drug mass characterized by the mass transfer rate to compartment j, including the elimination through metabolism (k_{i0}); and u_i represents the quantity the infused drug. Considering the volume of each compartment, the evolution of the concentrations in the different compartments can be mathematically modelled using Equations (2)–(5).

$$V_1 \frac{dC_1(t)}{dt} = V_2 C_2(t) k_{21} + V_3 C_3(t) k_{31} - V_1 C_1(t)(k_{10} + k_{12} + k_{13}) + u(t) \quad (2)$$

$$V_2 \frac{dC_2(t)}{dt} = V_1 C_1(t) k_{12} - V_2 C_2(t) k_{21} \quad (3)$$

$$V_3 \frac{dC_3(t)}{dt} = V_1 C_1(t) k_{13} - V_3 C_3(t) k_{31} \quad (4)$$

$$\frac{dEc(t)}{dt} = C_1(t) k e_0 - C_e(t) k e_0 \quad (5)$$

Here, C_1, C_2, and C_3 represent the drug concentrations (in µg/mL) in the central, fast, and slow compartments, respectively, as a result of the infusion rate u. V_1, V_2, and V_3 represent the volumes (in mL) of the compartments [26]. k represents the mass transfer rate between two compartments (in min^{-1}), as shown in Figure 1.

The pharmacodynamic model fully describes the relationship between the drug concentration in the effect compartment, Ec, and its influence on a certain clinical variable, Y. The relationship between the exposure to a drug and the effect of the drug has been modelled as a nonlinear sigmoid function [27]. Thus, the Hill equation, also known as the Emax model, has been widely used in anesthesia for PD models, as shown in Equation (6).

$$Y(t) = Y_0 + (Y_{min} - Y_0) \frac{Ec(t)^{\gamma}}{Ec_{50}{}^{\gamma} + Ec(t)^{\gamma}} \quad (6)$$

Here, Y_{min} represents the minimum achievable value of the clinical variable Y, and Y_0 represents the initial value of the variable in the case where the drug has no effect. The nonlinear shape of the sigmoid curve is described by γ. The PD model is characterized by the effect site concentration corresponding to 50% of the maximal clinical effect, Ec_{50}.

The presented structures can be used for modelling the individual effects of propofol and remifentanil on a certain physical variable. Previous studies have focused on the parametric values in the PK–PD model for propofol anesthesia [28, 29]. However, the Schnider model has typically been used in clinical practice [30]. For remifentanil modelling, the Minto model has become popular, as it is applicable to a wide range of patient characteristics, such as age, gender, and lean body mass (LBM) [31].

2.2. Propofol and remifentanil interactions

Although propofol and remifentanil are used for different purposes during general anesthesia, pharmacological interactions between these drugs have been observed in DOH [32–35]. More precisely, additive interactions between propofol and remifentanil has been observed in clinical practice [36]. In this study, the inclusion of the propofol–remifentanil interactions in the BIS index is based on Bouillon's proposal presented in [37]. The additive effect of propofol and remifentanil is given by the following nonlinear equation.

$$BIS = BIS_0 + (BIS_{min} - BIS_0)\frac{\left(\frac{Ec_r}{Ec_{50r}} + \frac{Ec_p}{Ec_{50p}}\right)^{\gamma}}{1 + \left(\frac{Ec_r}{Ec_{50r}} + \frac{Ec_p}{Ec_{50p}}\right)^{\gamma}} \qquad (7)$$

The variables in (7) can be interpreted as the ones presented in (6), in which BIS is now the clinical variable to be modelled. In this study, Ec_r and Ec_p are obtained from the Minto and Schnider models, respectively, according to the values presented in Table 1.

The minimum reachable value of the BIS, i.e., BIS_{min}, is set as 9.8 [40]. The rest of the parameters in the PK–PD model are identified using the algorithm presented in this paper.

Schnider Model	
V_1 [l]	4.27
V_2 [l]	18.9 – 0.391 (*Age* - 53)
V_3 [l]	238
k_{12} [min^{-1}]	$1/V_1$ (1.29 – 0.024 (*Age*-53))
k_{13} [min^{-1}]	0.196
k_{21} [min^{-1}]	$1/V_2$ (1.29 – 0.024 (*Age*-53))
k_{31}[min^{-1}]	0.0035
k_{10}[min^{-1}]	$1/V_1$ (1.8 + 0.0456 (*WT* - 77) – 0.0681 (*LBM* - 59) + 0.0264 (*HT* - 177))
Minto Model	
V_1 [l]	5.1 – 0.0201 (*Age* - 40) + 0.072 (*LBM* - 55)
V_2 [l]	9.82 – 0.0811 (*Age* - 40) + 0.108 (*LBM* -55)
V_3 [l]	5.42
k_{12} [min^{-1}]	$1/V_1$ (2.05 – 0.0301 (*Age* - 40))
k_{13} [min^{-1}]	$1/V_1$ (0.076 – 0.0113 (*Age* - 40))
k_{21} [min^{-1}]	$k_{12}\ V_1/V_2$
k_{31}[min^{-1}]	$k_{13}\ V_1/V_3$
k_{10}[min^{-1}]	$1/V_1$ (2.6 – 0.0162 (*Age* – 40) + 0.0191 (*LBM* - 55))
LBM Males: 1.1 *WT* – 128 $(WT/HT)^2$	
LBM Females: 1.07 *WT* – 148 $(WT/HT)^2$	

Table 1. Parameter values for the Schnider and Minto models [38, 39]. WT: weight [kg]; HT: height [cm].

2.3. Interpatient and intrapatient variability

Although the Schnider and Minto models integrate information from covariate factors (age, weight, height, and gender), variations in the BIS response between different patients with similar characteristics (interpatient variability) and even for the same patient throughout different stages of the surgery (intrapatient variability) have been observed [41, 42]. These variabilities should be included in the model to achieve more accurate prediction for personalized drug administration. In clinical practice, different strategies have been proposed to deal with this problem. In [43], the researchers considered age as a differentiating factor for patients in proposing an automatic controller for propofol titration. Other strategies are based on online identification and estimation of the parameters to deal with both interpatient and intrapatient variability [44]. However, these models are mainly based on short-time predictions of the BIS. Consequently, the algorithm presented in this paper is applied iteratively to update the parameters of the PK–PD model according to the real evolution of the patient.

2.4. Time delay in BIS signal

The BIS monitor is widely used in clinical practice for measuring the DOH. It is based on the frontal EEG analysis and computes an index that ranges from 0 to 100. This monitor has been proposed as the feedback variable in the closed-loop control of hypnosis. However, one of the main limitations in using this device is the introduction of an important source of delay in the process. The main reason for this is the presence of artifacts during the surgery that reduce the quality of the signal. Thus, the monitor processes the measurements using mathematical algorithms that introduce variable time delays. Researchers have attempted to overcome this problem, which becomes critical when a closed-loop strategy is implemented [45–47]. The identification algorithm proposed herein considers the presence of the variable time delay while identifying the PK–PD parameters.

3. Optimization-based identification algorithm

The main objective of the proposed algorithm is to identify the parameters involved in the PK–PD structure for BIS modelling in propofol–remifentanil anesthesia. In particular, this algorithm deals with

i) interpatient and intrapatient variabilities,
ii) propofol-remifentanil interactions, and
iii) variable time delays introduced by the BIS monitor.

To this end, the structure of the PK–PD model presented in Equation (7) is employed for BIS prediction in this study. The variable time delay introduced by the monitor is identified for the model characterization. Thus, the parameters to be determined during the optimization are

$$\theta = \{Ec_{50p}, Ec_{50r}, Ke_{0p}, Ke_{0r}, \gamma, L\}, \quad (8)$$

where p and r represent propofol and remifentanil, respectively, and L represents the time delay (in s) introduced by the BIS monitor. The goal is to minimize the error between the real evolution of the BIS observed during clinical practice and the BIS evolution predicted by the

model. Considering the nonlinearity introduced in the PD model through the Hill function, the algorithm is based on a nonlinear least-squares solver that attempts to minimize the expression

$$\min_{\theta}\left\|F(\theta,u_p,u_r)-BIS\right\|_2^2=\min_{\theta}\sum_i\left(F(\theta,u_{p_i},u_{r_i})-BIS_i\right)^2, \quad (9)$$

where u_p and u_r represent the propofol and remifentanil infusion rates, respectively, and F corresponds to Equation (7). The trust-region reflective algorithm was used. This is a subspace trust-region method based on the interior-reflective Newton method [48]. The upper and lower bounds for θ were considered, as shown in Table 2, according to previous research [29, 37].

Parameter	Range
Ec_{50p} [mg/l]	2.0–5.5
Ec_{50r} [ug/l]	5.0–40
Ke_{0p} [min^{-1}]	0.1–0.55
Ke_{0r} [min^{-1}]	0.1–0.8
γ	0.5–2.5
L [s]	10–150

Table 2. Upper and lower bounds for the optimization of θ.

The anesthetic process is commonly divided into three stages: induction, which involves loss of consciousness; maintenance, in which the surgery is performed; and emergence, when the drug titration ceases and the patient recovers from the surgery. However, most of the proposed control strategies focus on the maintenance stage. Regulators aim to keep the BIS value within a safe range, minimizing the effects of disturbances during the surgery. Thus, this algorithm was principally developed to make predictions during the maintenance phase. Accordingly, the general scheme for the application of the presented identification algorithm was divided into the following two parts.

Induction phase: This part consists of a preliminary identification of the parameters, θ, as the starting point for the prediction during the maintenance stage. The induction phase includes data from the beginning of the drug infusion to the instant at which the BIS of the patient reaches 50. The BIS_0 parameter in (7) is computed in this phase as the mean of the BIS values before

the induction. This stage provides the first parameterization of the model before starting the predictions during the maintenance phase.

Maintenance phase: Once the maintenance phase starts, the algorithm predicts the evolution of the BIS considering the model previously identified. This model is kept until the values of the predicted BIS, $F(\theta, u_p, u_r)$, and the real BIS from the clinical data differ by >10% for 5 min. The prediction error for the last 5 min is computed as follows:

$$error = \frac{\left|mean(BIS_5) - mean(BIS_{p5})\right|}{mean(BIS_5)} \cdot 100\ [\%] \tag{10}$$

Here, BIS_{p5} and BIS_5 represent the predicted and real BIS values, respectively, for the last 5 min. If *error* > 10%, the identification algorithm is run again, considering the more recent information of the clinical data for θ identification. Thus, an updated model for BIS prediction is obtained. The data considered for the new identification of the model include (at least) the evolution of the BIS for the last 5 min. If no change in the infusion rates has been observed in the last 5 min, the algorithm increases the time range considered until the last variation of any of the drugs (u_p or u_r) is included in the identification. The updated model is kept for the next 5 min (at least). Then, the prediction error is recomputed. A schematic summarizing this process is presented in Figure 2.

To evaluate the quality of the presented strategy, the prediction mean square error (PMSE), median performance error (MDPE), and median absolute performance error (MDAPE) [49] were calculated using Equations (11)–(13).

$$PMSE = \frac{1}{N}\sum_{i=1}^{N}\left(BIS_i - BIS_{p,i}\right)^2 \tag{11}$$

$$MDPE = median\left\{\frac{BIS_i - BIS_{p,i}}{BIS_{p,i}} \cdot 100\%\right\}_{i=1,\ldots,N} \tag{12}$$

$$MDAPE = median\left\{\left|\frac{BIS_i - BIS_{p,i}}{BIS_{p,i}}\right| \cdot 100\%\right\}_{i=1,\ldots,N} \tag{13}$$

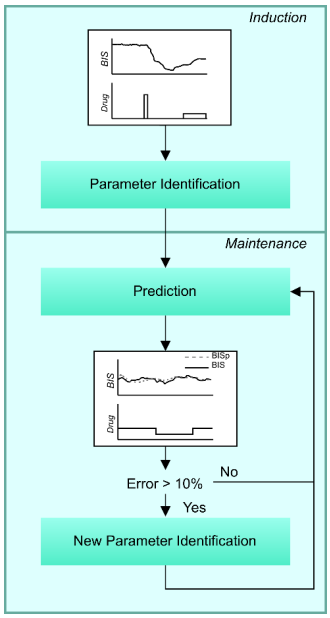

Figure 2. Proposed algorithm for the adaptive identification of the PK–PD model.

The proposed methodology is applied individually to each patient undergoing general anesthesia. This scheme deals with interpatient variability, as an individualized parameterization of the PK–PD model is proposed according to the real clinical response of each patient. Additionally, this parameterization is updated throughout the surgery according to the prediction error; thus, the algorithm can detect not only intrapatient variabilities but also the variable time delay and can adapt the parameters of the model accordingly.

4. Clinical data

To evaluate the proposed identification algorithm, clinical data from a pilot prospective observational study conducted at the Hospital Universitario de Canarias were used. Seventeen adult patients of ASA Status I–III scheduled for cholecystectomy surgery were enrolled in this study. All the patients received an informative document about the study and gave informed consent. All the surgeries followed the same clinical protocol. TIVA with propofol (hypnotic

agent) and remifentanil (analgesic agent) was performed for induction and maintenance of general anesthesia. Two intravenous Graseby 3500 pumps were used. A constant intravenous infusion of remifentanil at a rate of 0.2 μg/kg was started 7 min before the induction. Subsequently, a propofol intravenous bolus at the maximum rate of the pump (1200 mL/min) was administered for induction. For assessing the hypnotic level of the patients, a BIS A2000 VISTA monitor (Aspect Medical, USA. VISTA Application: 3.22) was used. A BIS noninvasive Quatro four-electrode sensor was applied to the patient's forehead to collect the raw EEG data during the surgery. The anesthesiologist varied the propofol infusion rate manually to reach a BIS target of 50. The remifentanil dose was adjusted depending on the autonomic reaction of the patient (variations in heart rate or arterial pressure) or for preventing the effects of surgical events. Only 0.05–0.10 μg/kg/min remifentanil increments or decrements were allowed.

During the surgery, the BIS, propofol infusion rate (mg/kg/h), and remifentanil infusion rate (μg/kg/min) were automatically registered every 5 s using software. An application for this was previously developed in MATLAB. A laptop ran the application during the surgeries. The BIS monitor, as well as both infusion pumps, were connected to the laptop via RS232 interfaces. Finally, all the data recorded during the surgeries were saved as .mat files for the analysis. An example of the data captured during a surgery is shown in Figure 3.

5. Results

The proposed identification algorithm was used to model the clinical response of the patients recorded from the 17 surgeries. First, the parameters of the model for the induction stage were estimated. The mean values and standard deviations of the parameters identified in the optimization are presented in Table 3.

As an illustrative example, a comparison between the measured BIS signal and the model output for one of the patients is presented in Figure 4. It is observed that the general trend was satisfactorily described by the model. Similar results were obtained for the other patients enrolled in this study. The error between the real BIS and the outputs of the identified models

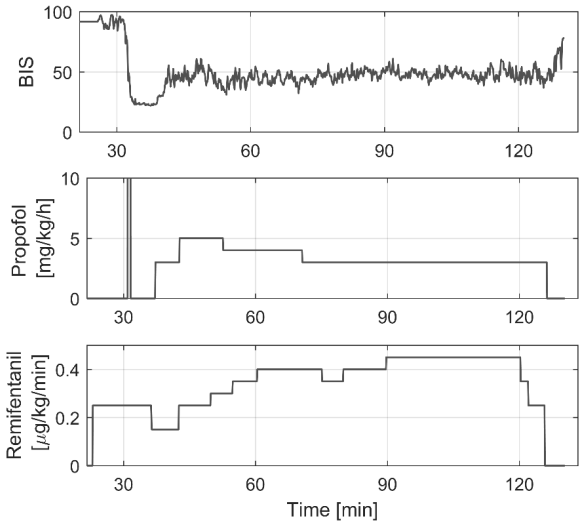

Figure 3. Evolution of BIS and the propofol and remifentanil infusion rates during one of the surgeries.

Ec_{50p} [mg/l]	Ec_{50r} [µg/l]	Ke_{0p} [min^{-1}]	Ke_{0r} [min^{-1}]	γ	Delay [s]
3.364 (1.578)	21.761 (15.194)	0.220 (0.123)	0.311 (0.326)	1.924 (0.611)	35.59 (17.22)

Table 3. Values of the parameters identified from the adjustment of the induction stage after applying the proposed algorithm to the 17 patients. The values are expressed as mean (standard deviation (SD)).

during the induction phase is presented in Figure 5. The errors were normalized according to the maximum value per type of error that was reached for the 17 patients during the induction.

The algorithm was then used for the prediction of the BIS index during the maintenance phase. On average, the identification algorithm was run every 11.63 (5.37) min to update the parametric model as a consequence of the prediction error exceeding 10%. The mean values of the identified parameters throughout the 17 surgeries are presented in Table 4.

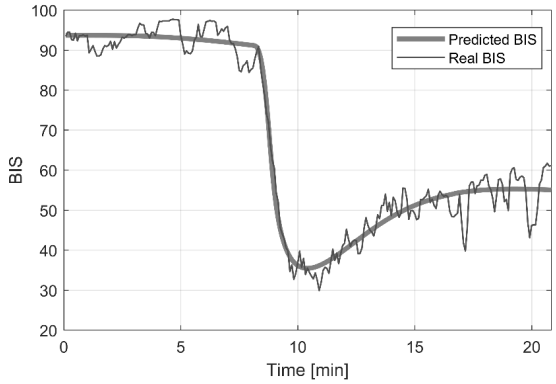

Figure 4. Comparison between the real BIS and the output of the model for one patient in the induction stage.

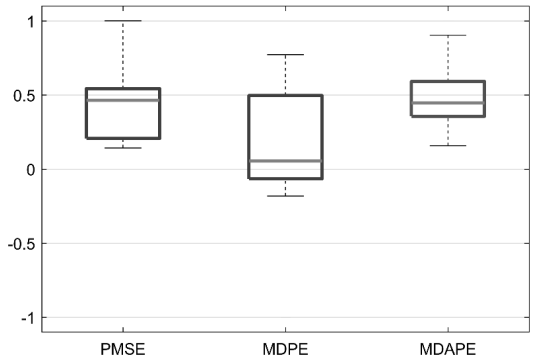

Figure 5. Measured error indices during induction. The errors are normalized with respect to the maximum values (PMSEmax = 61.06; MDPEmax = –4.18; MDAPEmax = 9.34).

Ec_{50p} [mg/l]	Ec_{50r} [µg/l]	Ke_{0p} [min^{-1}]	Ke_{0r} [min^{-1}]	γ	Delay [s]
3.127 (1.241)	14.914 (10.172)	0.261 (0.150)	0.262 (0.200)	1.861 (0.621)	63.6 (41.7)

Table 4. Values of the parameters identified from the prediction of the maintenance stage after applying the proposed algorithm to the 17 patients. The values are expressed as mean (SD).

Figure 6 shows an example of the application of the adaptive algorithm to one of the patients. The prediction errors in the maintenance phase are presented in Figure 7. Larger errors were obtained when comparing the maintenance phase with the induction phase. This is because the errors presented in Figure 5 are fitting errors, as the outputs of the models were compared with the same clinical data that were used for parameter identification during the induction. However, the errors shown in Figure 7 indicated the predictive capability of the adaptive model during the maintenance phase. In this case, the prediction of the model was compared with the real evolution of the BIS once the model was updated according to previously available data.

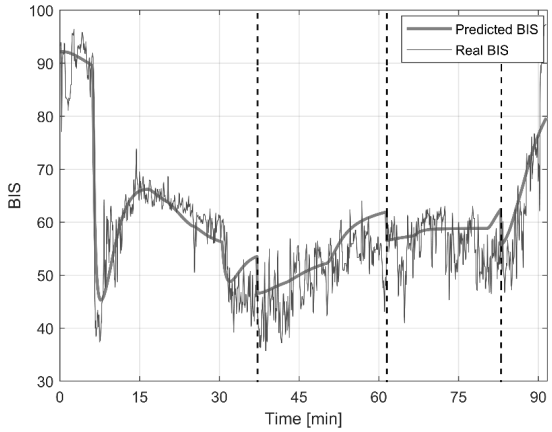

Figure 6. Comparison between the real BIS and the predicted BIS for one patient in the induction + maintenance stages. The dashed lines represent the instants at which the parametric model was adapted.

Finally, to evaluate the suitability of including an adaptive model for BIS prediction in anesthesia, we compared the prediction errors of the previously identified models with the prediction errors of static models whose parameters were only identified at the beginning of the maintenance phase. In this new case, the parameters of the models were only identified once, including information from the first 10 min of the maintenance phase. To this end, we applied the same optimization technique. A comparison of the errors for this new scenario is presented in Figure 8. Smaller errors and variations were observed when considering the proposed adaptive models. This fact indicates the importance of using an adaptive model for BIS

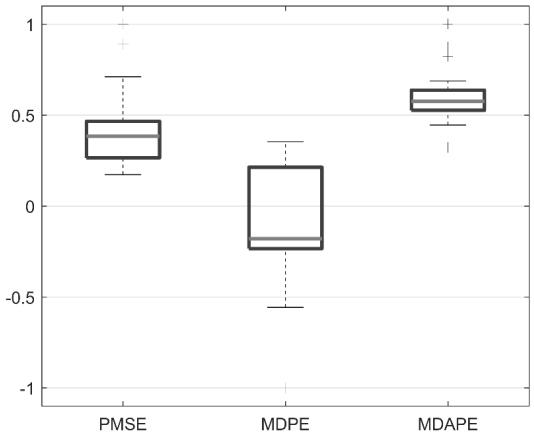

Figure 7. Measured error indices during maintenance. The errors are normalized with respect to the maximum values (PMSEmax = 143.41; MDPEmax = –14.05; MDAPEmax = 17.01).

prediction that is capable of dealing with the possible variations that can occur throughout the surgery.

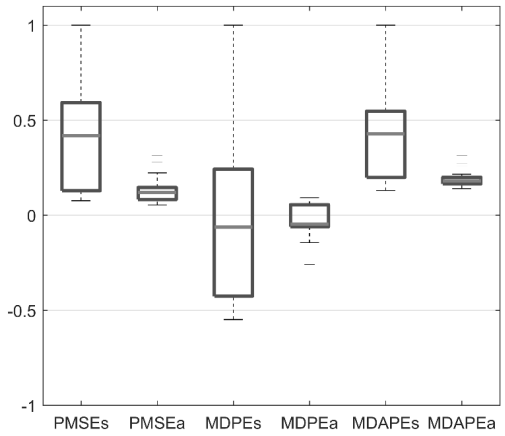

Figure 8. Comparison of the error distribution for a static model (s) and an adaptive model (a). The values are normalized considering the absolute maximum values of PMSE = 458.06, MDPE = 54.28 and MDAPE = 54.28 obtained via both methodologies.

6. Discussion

The application of the proposed algorithm resulted in individualized identification of the PK–PD models, adjusted to the clinical response of each patient for BIS prediction in propofol–remifentanil anesthesia. The proposed model structure together with an optimization-based identification algorithm led to adaptive models capable of dealing with patient variabilities, propofol–remifentanil interactions, and the variable time delay introduced by the BIS monitor. On one hand, the differences observed between the parameters identified during the induction and maintenance phases evidenced the presence of variations in the response of the patient throughout the surgery. Additionally, the large errors between the proposed scheme and a non-adaptive algorithm indicated the convenience of implementing an adaptive methodology to deal with variabilities occurring during the anesthetic process. On the other hand, the standard deviations of the parameters identified from the induction phase confirmed the presence of variabilities when comparing the clinical responses of different patients, mainly derived from the interpatient variability.

To validate the results of this study, we compared the identified parameters shown in Tables 3 and 4 with previous proposals. To the best of our knowledge, this is the first study in which drug interaction, inter/intra patient variabilities, and the variable time delay introduced by the BIS monitor have been included simultaneously for BIS modelling. We compared the identified Ec_{50p} and Ke_{0p} parameters with values obtained in previous studies related to propofol–remifentanil anesthesia. Similar results were obtained in [40] when comparing the mean Ec_{50p} for the induction phase (3.364 (1.578) vs. 3.35 (2.79–3.91)). For the maintenance stage, the identified parameters Ec_{50p} (3.127 (1.241) vs. 3.4) and Ke_{0p} (0.261 (0.150) vs. 0.2) in [50] were similar to those reported herein. The main advantage of our method is that in the previous studies, neither the variable time delay of the BIS monitor nor the intrapatient variability factor was included. Additionally, we compared the parameters identified in previous clinical studies when considering the same expression to model the propofol–remifentanil additive interaction. In [37], slightly higher values of Ec_{50p} (3.127 (1.241) vs. 3.07), Ec_{50r} (14.914 (10.172) vs. 20.1), and γ (1.861 (0.621) vs. 1.43) were reported. These discrepancies could be because the previous study did not take into account the intrapatient variability affecting Ke_0. Thus, the Ke_{0p} and Ke_{0r}

values were not adapted during the surgery. Similar mean delay values of the BIS monitor have been reported. In particular, the time delay during the induction phase identified in [51] was similar to our results (35.59 (17.22) s vs. 30.09 ± 18.73 s).

Finally, the prediction errors of the proposed model were compared with those in previous reports. Generally, the presence of noise in the BIS signal resulted in lower performance when the real data were compared with the predictions of the identified models. In [52], similar measures of error were computed to validate the results obtained. Smaller PMSE, MDPE, and MDAPE values were obtained during the maintenance phase compared with our proposal. However, only one patient was used for the verification. Thus, the interpatient effect was not considered in the validation. Additionally, previous studies have mainly been based on short-term predictions [14]. Smaller prediction errors can be found in the literature. However, regarding the possibility of using this identification technique as a part of a model predictive controller strategy and considering the slow dynamics of these types of systems, the proposed method deals with longer prediction times. Thus, larger prediction errors are expected for the results of this study compared with those of the previously reported strategies.

Preliminary studies should be conducted before implementing our proposal for online estimation. Specifically, the overparameterization of the model can result in longer computational times. This fact should be considered if the model is implemented for MPC strategies. Nonetheless, the proposed algorithm is designed to be run every 5 min only if a divergence between the real data and the prediction of the model persists. Thus, running the optimization algorithm in parallel without degrading the performance of the closed-loop strategy is feasible.

7. Conclusions

We proposed a new optimization-based methodology to identify parametric PK–PD models for predicting the DOH level in propofol–remifentanil anesthesia. In contrast to previously published research, the proposed method can deal simultaneously with (i) both interpatient and intrapatient variabilities, (ii) propofol–remifentanil interactions, and (iii) variations in the time delay introduced by the BIS monitor. Consequently, this methodology improves previous

proposals, with two main contributions. First, the parametric model is updated throughout the surgery to capture the real evolution of the patient. This allows the system to deal with both intrapatient and interpatient variabilities. Second, all the factors likely to affect the anesthetic modelling process, such as the patient variability, drug interactions, and DOH monitor, are explicitly included in the model. To the best of our knowledge, this is the first proposal that includes all the factors that may affect the BIS modelling in general anesthesia.

The proposed methodology was tested satisfactorily on 17 patients. The parametric values identified for the resulting PK–PD models were compared with previously published clinical results. The aforementioned potential of using an adaptive strategy considering both intrapatient and interpatient variabilities was evidenced. These promising results indicated that the proposed method can be implemented in MPC controllers for closed-loop strategies. Specifically, the availability of adaptive models to predict the clinical response of the patient can outperform previously published research.

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Appendix B. Manuscript Under Review

Robust PID control of propofol anaesthesia: uncertainty limits performance, not PID structure

This Appendix presents the methodology proposed in this doctoral thesis for synthesizing the robust optimal filtered PID controller for propofol anesthesia. Then, the PID controller is compared with the Youla controller synthesized under the same technical and clinical considerations in order to evaluate the performance limitations.

Part of this work has been developed in collaboration with the Department of Automatic Control of Lund University and the Department of Electrical and Computer Engineering of The University of British Columbia.

Note: This article has been submitted to a scientific journal for publication.

Robust PID control of propofol anaesthesia: uncertainty limits performance, not PID structure

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Abstract

Background and Objective: New proposals to improve the regulation of hypnosis in anaesthesia based on the development of advanced control structures emerge continuously. However, a fair study to analyse the real benefits of these structures compared to simpler clinically validated PID-based solutions has not been presented so far. The main objective of this work is to analyse the performance limitations associated with using a filtered PID controller, as compared to a high-order controller, represented through a Youla parameter.

Methods: The comparison consists of a two-steps methodology. First, two robust optimal filtered PID controllers, considering the effect of the interpatient variability, are synthesised. A set of 47 validated paediatric pharmacological models, identified from clinical data, is used to this end. This model set provides representative interpatient variability. Second, individualised filtered PID and Youla controllers are synthesised for each model in the set. For fairness of comparison, the same performance objective is optimised for all designs, and the same robustness constraints are considered. Controller synthesis is performed utilising convex optimisation and gradient-based methods relying on algebraic differentiation. The worst-case performance over the patient model set is used for the comparison.

Results: Two robust filtered PID controllers for the entire model set, as well as individual-specific PID and Youla controllers, were optimised. All considered designs resulted in similar

frequency response characteristics. The performance improvement associated with the Youla controllers was not significant compared to the individually tuned filtered PID controllers. The difference in performance between controllers synthesized for the model set and for individual models was significantly larger than the performance difference between the individual-specific PID and Youla controllers. The different controllers were evaluated in simulation. Although all of them showed clinically acceptable results, the robust solutions provided slower responses.

Conclusion: Taking the same clinical and technical considerations into account for the optimisation of the different controllers, the design of individual-specific solutions resulted in only marginal differences in performance when comparing an optimal Youla parameter and its optimal filtered PID counterpart. The interpatient variability is much more detrimental to performance than the limitations imposed by the simple structure of the filtered PID controller.

Keywords: Depth of hypnosis; PID; Robust optimal control; Youla controller

1. Introduction

Adequate dosing of anaesthetic drugs is required to avoid awareness, maintain homeostasis, and reduce postoperative discomfort and recovery times in the post-anaesthesia care unit [1]. This requires continuous monitoring of the patient's anaesthetic state, enabling the anaesthesiologist to adapt drug titration as needed. This continous decision-making process has inspired extensive research on closed-loop control systems for anaesthetic drug dosing.

Research on closed-loop anaesthesia control has focused on the control of the hypnosis component of general anaesthesia, known as the depth of hypnosis (DoH) [2]. In a closed-loop structure, the controller manages the infusion rate of the intravenous anaesthetic drug to maintain a user-defined DoH setpoint. The most extensively evaluated DoH control systems have had the infusion rate of the anaestetic drug propofol as control signal, and the output of a cortical EEG monitor as measurement signal. Such monitors quantify the DoH on a scale between 0 to 100, where values close to 0 represent low cortical activity and values close to 100 represent awareness [3]. A DoH range corresponding to 40–60 is recommended for general anaesthesia [4]. In order to remain within this admissible range, the controller must deal with a

set of clinical considerations. Surgical stimuli disturb the DoH during anaesthesia. Thus, the controller needs to attenuate the effect of the surgical disturbances. Failure to do so can result in patient awareness and increase the risk of adverse haemodynamic responses, particularly in fragile patients [5]. The closed-loop system also needs to be insensitive to high frequency measurement noise typically associated with DoH monitors. Furthermore, and of high relevance to the design, the controller must be robust towards interpatient variability in response to therapy within the target population [6]. It is practically impossible to obtain an accurate model describing the response dynamics of an individual patient prior to commencing the drug infusion, which imposes an on achievable performance restriction [7].

Several controller types have been proposed within the DoH-propofol control context, of which some have been clinically evaluated [8]. Thanks to its simplicity, PID has become one of the most widely used controller types in this discipline. Properly tuned PID controllers have demonstrated adequate performance and safety in the clinical setting [9]. Simple structure and low parameter count are attractive features of the filtered PID controller, facilitating synthesis, implementation and verification. More complex controllers have also been developed and clinically tested [10, 11]. A significant increase in performance with maintained safety would motivate the consideration of more advanced controller types. However, establishing a fair comparison between controller types found in the literature is not straightforward. The design objectives commonly vary between published designs, and they are not always explicitly stated in works presenting manually tuned controllers. Furthermore, the sets of patient models used for controller synthesis vary across research groups, as does the dynamics on which the obtained controllers are evaluated. While published studies typically investigate the performance of a particular controller, they provide little insight into whether this performance is foremost limited by the type of controller or by some other factors such as the variability in the patient model set used for the synthesis. Thus, to establish a meaningful comparison between controller types, measures of performance, and robustness to deal with clinical demands must be harmonized.

The main objective of this work is to compare the performance achieved by using a filtered PID controller with that for a higher-order LTI controller. This study proposes the synthesis of the Youla parameter to provide an upper bound on performance increase when moving filtered

PID to an LTI controller of arbitrary order. A synthesis formulation producing robust controllers, capable of both minimizing the effect of surgical stimuli on the DoH and handling the interpatient variability, is considered.

While methods for optimising filtered PID controllers over sets of plant models are considered herein, there exists no known method to design optimal LTI controllers for a set of process dynamics [12]. Therefore, a two-step comparison was proposed. First, the effect of the interpatient variability on the closed-loop performance was studied. The performance achieved by a robust optimal PID synthetized for a set of patients was compared with that achieved by individualized optimal PID controllers. Second, the performance of individualised PID controllers was compared with that of individual Youla parameters for the models in the considered set.

To our knowledge, this is the first systematic comparison between a filtered PID controller and an optimal LTI controller for DoH control, where both controllers have been synthesized using the same performance criteria and robustness constraints.

2. Modelling the anaesthetic process

2.1. PK–PD models

Pharmacokinetic-pharmacodynamic (PK-PD) models are used in anaesthesia to describe the relationship between the hypnotic drug (propofol) infusion rate, and its effect on a clinical variable (the DoH) [13]. The comparison presented in this work was made using a set $\mathcal{P}$ of 47 validated paediatrics PK-PD models [14]. The models were identified from clinical data and then linearised around the operating point as described in [15].

Although variability was characterised directly by the linearised models of the set $\mathcal{P}$, a more conservative characterisation of the model set variability was provided by the unstructured additive uncertainty model

$$P_\Delta(i\omega) = \{P_0(i\omega) + \rho(\omega)\Delta;\ \ \Delta \in \mathbb{C}, \|\Delta\|_\infty < 1\}, \qquad (1)$$

where P_0 is a nominal model, Δ is any point within the unit disc in the complex plane, and ρ is the uncertainty radius. The response $P_\Delta(i\omega)$ was chosen to frequency-wise minimise $\rho(\omega)$, while covering $\mathcal{P}(i\omega)$. This results in a convex program, enabling efficient computation of P_0 and ρ from $\mathcal{P}$, as described in [16]. Both $\mathcal{P}$ and P_Δ were considered as descriptions of interpatient variability in our study.

2.2. Equipment models

The Bispectral Index (BIS) monitor has been used to measure the DoH in a majority closed-loop controlled propofol anesthesia systems [17]. We instead assume the use of the NeuroSense WAV_{CNS} monitor. It is similar to the BIS, but comes with the advantage of time-invariant response dynamics [18]

$$M(s) = \frac{1}{(8s+1)^2}, \tag{2}$$

making it more suitable for closed-loop control applications [19]. The monitor dynamics (2) were incorporated in our study through series connection with the patient model.

Dynamics of modern remote-controlled infusion pumps are essentially static and linear, with negligible quantisation effects. In addition, bandwidth and titration precision of these pumps are high, relative to the requirements imposed on a closed-loop propofol anaesthesia system. Consequently, no explicit actuator model has been employed.

2.3. Disturbance models

Two main exogenous disturbances were considered in this study. First, surgical stimuli act as disturbances, increasing the DoH, unless counteracted. As suggested in [20], they were modelled as steps added to the patient output. Second, measurement noise was added to the DoH monitor output. A white noise model, previously identified from data [20], was used.

3. Optimisation-based controller design

3.1. Performance and robustness

A block diagram illustrating the closed-loop system is shown in Figure 1. The control objective was to attenuate the disturbance, *d*, from the DoH, *z*. Considering that sudden large deviations from the setpoint are clinically worse than more persistent small setpoint deviations, the $\mathcal{L}_2$ norm of the monitored DoH, *y*, resulting from a disturbance step, *d*, was minimized.

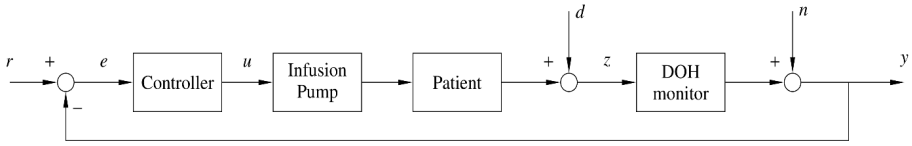

Figure 1. Block diagram of the closed-loop system. The signals are: DoH setpoint, *r*; propofol infusion rate, *u*; DoH, *z*; measured DoH, *y*; surgical disturbance, *d*; measurement noise, *n*.

To ensure robustness of the design, $\mathcal{H}_\infty$ constraints on the sensitivity function *S*, and its complement, $T = 1 - S$, were imposed. Constraining $\|T\|_\infty$ and $\|S\|_\infty$ provides robustness to additive process perturbations and loop-transfer perturbations [21]. Measurement noise was attenuated by imposing an $\mathcal{H}_2$ constraint on the transfer function *KS* from noise, *n*, to control signal, *u*. The noise sensitivity constraint was expressed using the $\mathcal{H}_2$, since the outcome of limiting the $\mathcal{H}_\infty$ norm depends heavily on for which frequency, with respect to the closed-loop bandwidth, it is attained [22]. The constraint levels (M_s, M_t and M_{ks}) were chosen to match worst case values of the constrained functions, evaluated over the considered interpatient variability model, with a previously clinically evaluated PID controller in the loop [23]. Furthermore, response undershoot was limited to 10 WAV_{CNS}, preventing the worst-case undershoot associated with the 50 WAV_{CNS} to bring the DoH outside the recommended 40–60 WAV_{CNS} interval for general anaesthesia. With modern infusion pumps, prevention of actuator wear is not a motivation for limiting control signal noise. However, slew rate limitations and the risk of the supervising anaesthesiologist putting a controller with violently varying output into manual mode would be [24].

Filtered PID controllers, robust over the model set, $\mathcal{P}$, and the uncertain model, P_Δ, were synthesised, alongside individual filtered PID controllers for each of the 47 models in $\mathcal{P}$. The latter were compared with Youla parameters, individually optimised for the same 47 models. First, this comparison quantified the benefit of increasing controller order. Second, the comparison between the individualised PID controllers with those optimized to be robust over $\mathcal{P}$ and P_Δ, respectively, quantified the performance limitations imposed by interpatient variability. Main considerations for the optimisation of the different controllers are presented in the next subsections

3.2. PID controllers

A general description for the synthesis of the PID controllers included in the comparison is presented in this section. Robust filtered PID controllers on the form

$$K(s) = C(s)\,F(s) \tag{3}$$

$$C(s) = k_p + k_i\frac{1}{s} + k_d s \tag{4}$$

$$F(s) = \frac{1}{T^2 s^2 + 2\zeta T s + 1} \tag{5}$$

were synthesised. Parameters [k_p, k_i, k_d] of the PID controller (4) were co-optimised with parameters [T, ζ] of the filter (5).

The parametrisation of K resulted in a non-convex synthesis problem that was approached with a two-stage method. First, a global optimisation, based on simulated annealing (SA), was performed [25], with logarithmic barrier functions representing the constraints. Since SA is a gradient-free method, it provides no means to verify local optimality. Consequently, the second stage comprised gradient-based optimisation by means of the method of moving asymptotes (MMA) [26]. The optimisation methods were implemented using the Julia language package ControlSystems.jl [27] in combination with forward-mode automatic differentiation [28]. Key implementation aspects are reviewed in [29].

The optimisation was performed over a uniform frequency grid

$$\Omega = \{\omega_1, \ldots, \omega_N\},\ \omega_k = \frac{k\pi}{NT_s},$$

where the number of frequency points, $N = 2^{11}$, was numerically verified to lie sufficiently dense for the problem at hand. The sampling period was set to $T_s = 5$ s, matching the actuation interval in the control system for which the models are intended [23].

3.2.1. PID control based on the model set

The filtered PID controller was optimised by maximizing the worst-case performance over the patient model set $\mathcal{P}$ while satisfying robustness and undershoot constraints for each patient model in $\mathcal{P}$:

$$\begin{aligned} &\min_{K} \quad \max_{\forall k \in \{1,\ldots,\#(\mathcal{P})\}} \left\| S_k \frac{1}{i\omega} \right\|_2^2 \\ &\text{subject to} \\ &\forall k \in \{1,\ldots,\#(\mathcal{P})\} \qquad \|S_k\|_\infty \le M_s \\ &\qquad\qquad\qquad\qquad\quad \|T_k\|_\infty \le M_t \\ &\qquad\qquad\qquad\qquad\quad \|KS_k\|_2 \le M_{ks} \\ &\qquad\qquad\qquad\qquad\quad \mathcal{F}^{-1}\left(S_k \frac{1}{i\omega}\right) \ge m_y. \end{aligned} \tag{6}$$

3.2.2. PID control based on the uncertain model

Interpatient variability was represented by $P_\Delta(i\omega)$, describing the set of all possible responses at frequency ω. The problem of optimisation of the worst-case performance while satisfying worst-case constraints over $P_\Delta(i\omega)$ is given by

$$\min_{K} \quad \frac{1}{\pi}\int_0^\infty \bar{S}^2 \frac{1}{\omega^2} d\omega \tag{7}$$

$$
\begin{aligned}
&subject\ to \\
&\forall\omega
\end{aligned}
\qquad
\begin{aligned}
&|P_0KM+1|-\rho|KM|-\frac{1}{M_s}\geq 0\\
&|P_0KM+f(M_t)|-\rho|KM|-\frac{f(M_t)}{M_t}\geq 0\\
&\|K\bar{S}\|_2\leq M_{ks}\\
&\min_{P_\Delta}\left(\mathcal{F}^{-1}\left(S_\Delta\frac{1}{i\omega}\right)\right)\geq m_y,
\end{aligned}
$$

where $$f(M_t)=\frac{M_t^2}{M_t^2-1}$$

and $$\bar{S}=\frac{1}{|P_0KM+1|-\rho|KM|} \qquad (8)$$

represents the worst-case sensitivity in terms of the optimisation objective generated by P_Δ. A detailed explanation of the derivations for the worst-case expressions in (7) and (8) is provided in the Appendix.

The last inequality of (7), where S_Δ represents any frequency-wise realisation of $(1 + PK)^{-1}$ with $P \in P_\Delta$, limits load-response undershoot to m_y. Minimisation under P_Δ generates the worst case for the constraint under S_Δ. Undershoot was limited by enforcing that $y_k \geq m_y$ is fulfilled for each corresponding time-domain sample

$$y_k = \frac{1}{N}\sum_{n=0}^{N-1} Y_n e^{\frac{2\pi n}{N}i} \qquad (9)$$

of the response y. Each Y_n needs to be selected from a disc in the complex plane, generated by P_Δ, before the inverse Fourier transform (9) is applied. The radii of these discs are given by the expression (A.6), provided in the Appendix. The smallest contribution to y_k from disc y_N is ρ_n, resulting in the bound

$$y_k \geq y_{k,0}\sum_{n=0}^{N-1}\rho_n. \qquad (10)$$

3.2.3. PID control based on the individual models

A similar formulation to (6) was considered for the optimisation of the individualised filtered PID, in which maximisation over $k \in \{1, \ldots, \#(\mathcal{P})\}$ was replaced by optimising individual controllers for each patient model *k*.

3.3. Youla synthesis

The Youla parameterisation characterises all stabilising controllers, *K*, for a linear plant, *P*. Using a suitable representation of a general controller transfer function, it is possible to apply convex optimisation to search for the optimal controller. For a stable plant, the Youla parameterisation becomes particularly simple. Introducing the Youla parameter

$$Q = \frac{K}{1 + PK}, \tag{11}$$

the sensitivity function and its complement can be expressed as

$$T = PQ \tag{12}$$

$$S = 1 - PQ \tag{13}$$

while the control signal response to measurement noise is given by $KS = Q$.

Transient responses were evaluated over T = 8000 s, being a sufficient horizon considering propofol PK dynamics. The Youla parameter Q was expressed using the Ritz approximation

$$Q_d(z) = Q_0(z) + \sum_{k=1}^{Nq} x_k Q_k(z) \tag{14}$$

where x_k are the scalar variables to be optimised, and $Q_k(z) = z^{k-1}$ represents a discrete-time shift. The constant term of (14) is given by

$$Q_0(z) = \frac{K_{ind,d}(z)}{1 + P_d(z)K_{ind,d}(z)}, \tag{15}$$

where

$$K_{ind,d}(z) = \mathcal{FOH}(K_{ind}(s), T_s) \tag{16}$$

$$P_d = \mathcal{FOH}(P(s), T_s) \tag{17}$$

are the first-order-hold discretisations of the optimal individualised filtered PID controller and the plant, respectively.

The same frequency grid and sampling period were used for the Youla and filtered PID designs. The corresponding cost to be minimised was

$$J = \sum_{k=0}^{T/T_s} y^2(k) \tag{18}$$

The aforementioned robustness constraints on *S*, *T* and *KS*, as well as the undershoot constraint on *y* were introduced. To guarantee that *J* converges as $t \to \infty$, the controller must have integral action. This was enforced by adding the steady-state constraint

$$\left| Q_d(1) - \frac{1}{P_d(1)} \right| < \varepsilon \tag{19}$$

for some small ε (10^{-7} was used here). All considered constraints are closed-loop convex, meaning that a solution can be found efficiently. Once the optimal Q_d is found, the controller is recovered as

$$K_d = \frac{Q_d}{1 - Q_d P_d}. \tag{20}$$

The optimisation problem was specified and solved in MATLAB using the CVX optimisation library with the MOSEK solver. All solutions were checked for constraint violations between grid point.

4. Results

4.1. Analysis of the optimisation

Table 1 provides an overview of the resulting controllers. The parameter values obtained through the optimisation are shown in Table 2 for the robust filtered PID designs. The choice of $N_q = 400$ parameters of the Youla controller, Q_K, was deemed sufficient, and further increase resulted in negligible performance gain. Since the high parameter count of Q_K renders tabulation infeasible, Bode plots for the analysis of the frequency response of each controller are presented instead. Figure 2 reveals a high degree of similarity between the considered designs. The main difference between the individually optimised PID controllers, K_{ind}, and their Youla parameter counterparts, K_Q, lies in the mid-frequency range, where the additional degrees of freedom of K_Q provided a phase advance in the range of 0.01–0.05 rad/s. The main difference between the filtered PID designs were for low frequencies.

Controller	Colour	Description
K_{set}	Blue	PID for patient set
K_Δ	Orange	PID for additive uncertainty model
K_Q	Green	Individualised Youla controller
K_{ind}	Violet	Individualised PID controller

Table 1. List of evaluated Youla parameters and filtered PID controllers, and the colour used to represent them in figures of Section 4.

	K_p	T_i	T_d	T_f	ζ
K_{set}	1.04	314	65.1	15.3	0.71
K_Δ	1.05	644	38.7	11.1	0.73

Table 2. Parameters of the considered filtered PID controllers. Parameters correspond to the ideal serial PID form $Kp\,(1 + (T_i s)^{-1} + T_d s)$. The filter parameters are presented as in (5). Units are: Kp [mg/kg/min WAV_{CNS}]; Ti [s]; Tf [s]. The relative damping ζ is dimensionless.

Figure 3 shows the distribution of the optimisation cost when applying the considered controllers over the patient model set $\mathcal{P}$. Cost values were normalised by the maximum cost $\alpha = 316$, attained over $\mathcal{P}$ with the clinically verified filtered PID controller, K_C. For a particular

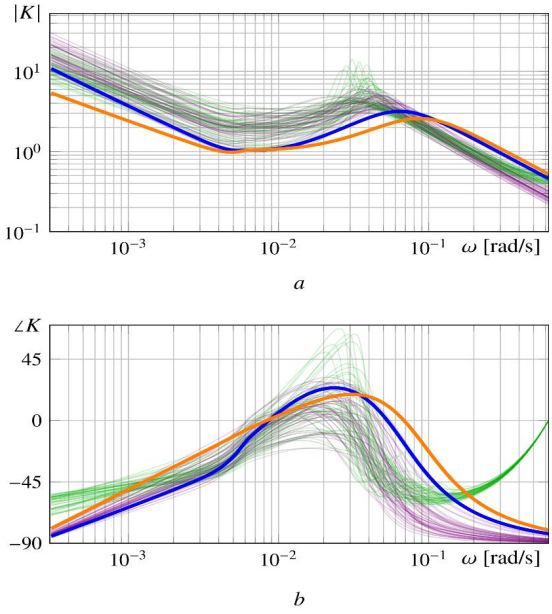

Figure 2. Controller Bode plots. *a*) shows magnitude, $|K(i\omega)|$; *b*) shows phases, $\angle K(i\omega)$. Colours according to Table 1.

model, it was observed that there was very little room for performance improvement when optimising a Youla controller compared to an individually tuned filtered PID controller. However, including uncertainty from the interpatient variability resulted in a significantly worse performance as seen by comparing either of K_{set} or K_{Δ} with K_{ind}.

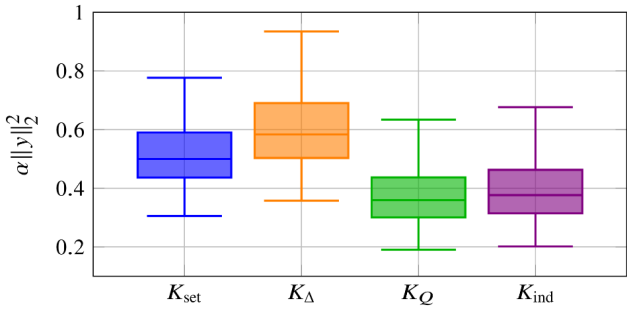

Figure 3. Distribution of optimisation cost $\|y\|_2^2$ over the patient model. Colours according to Table 1.

Resulting sensitivity and complementary sensitivity magnitudes are shown in Figure 4. The constraint levels, M_s = 2.55 and M_t = 2.08, correspond to the worst case $\mathcal{H}_\infty$ norms obtained when evaluating K_C over $\mathcal{P}$. The $\mathcal{H}_2$ norms and the Bode magnitudes of the underlying KS were computed for the analysis of the noise sensitivity constraint. Results are shown in Figures 5 and 6, respectively. The noise sensitivity constraint was active for each controller type except K_Δ. Specifically, it was active for each of the 47 models in $\mathcal{P}$ under K_{ind} and K_Q. In addition, at least one patient model of the set reached the constraint when optimising K_{set}. As a result, it could be noted that the performance was limited by the constraint level on noise sensitivity, KS, in three of the four proposed designs.

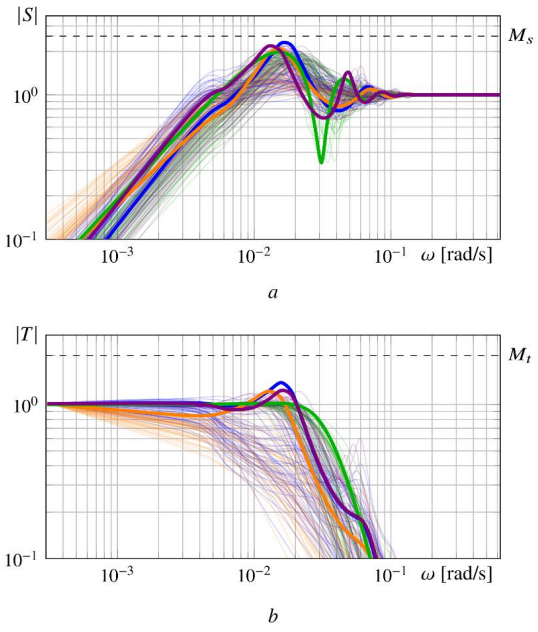

Figure 4. Magnitudes of *a*) sensitivity $|S(i\omega)|$and *b*) complementary sensitivity $|T(i\omega)|$for the considered designs. The horizontal dashed black line shows the constraint levels. Thick lines show the worst-case constraint level for each considered controller type. Colours according to Table 1.

The results of the closed-loop patient output to a step disturbance when considering the linearised patient models is shown in Figure 7. The undershoot constraint was only active for

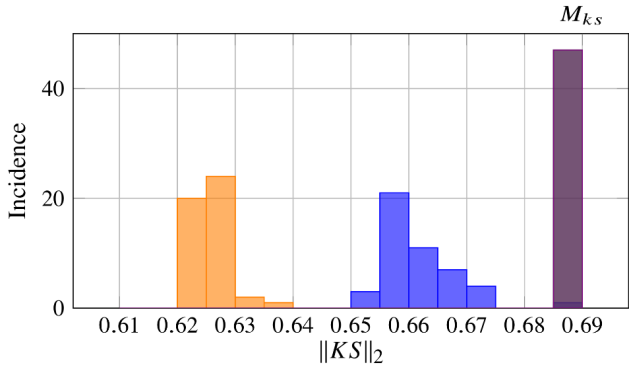

Figure 5. Distribution of noise sensitivity $\mathcal{H}_2$norm, $\|\mathrm{KS}\|_2$, of the considered controllers over the patient model set. The vertical dashed black line shows the constraint level, M_{KS}. Colours according to Table 1.

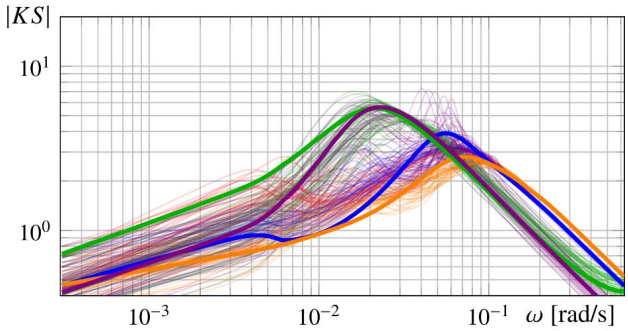

Figure 6. Noise sensitivity magnitude $|K(i\omega)S(i\omega)|$for the considered design. Thick lines correspond to the closed-loop generating the worst $\|\mathrm{KS}\|_2$ for each controller type. Colours according to Table 1.

K_Δ. However, as a consequence of Δ being a conservative uncertainty description, K_Δ resulted in fulfilment of the undershoot constraint when evaluating the controller over the 47 individual patient models of $\mathcal{P}$.

4.2. Simulations

To further investigate the clinical feasibility, the obtained controllers were evaluated in a simulation using the 47 nonlinear patient models, from which the linear models comprising

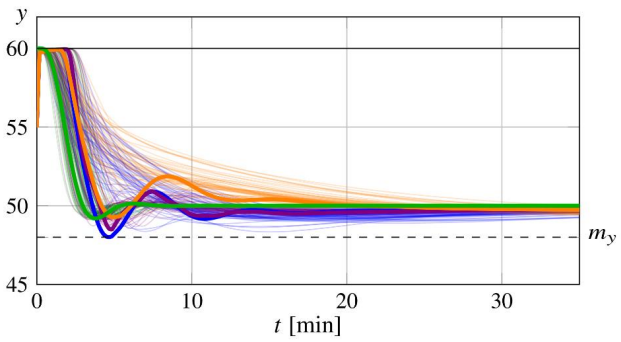

Figure 7. Closed-loop response y(t) resulting from applying an additive output disturbance of magnitude 10 WAV_{CNS} (solid black line) to each model in the set. Thick lines show the responses of maximal undershoot for each considered controller type. The dashed black line shows the undershoot constraint level m_y. Colours according to Table 1.

were obtained. A DoH setpoint of 50 WAV_{CNS} was considered. With the systems in stationarity at this setpoint, a step disturbance of magnitude 10 WAV_{CNS} was applied at t = 0. The outcome is shown in Figure 8. All designs provided admissible disturbance responses. Expectedly, the robust controllers responded slower than the individualized ones.

5. Discussion

This simulation study has compared the achievable performance of a widely used and clinically validated PID-based structure for DoH control to that involving a more advanced linear time-invariant controller of arbitrary high order. All considered controllers were optimised using the same performance and robustness criteria. The effect of the interpatient variability on the performance was analysed. Both synthesis and evaluation were based on a set of previously published and verified PK-PD patient models. All the designs were performed for linearised versions of the patient models. Consequently, the resulting controllers were evaluated together with the underlying nonlinear models to validate the results. The comparison showed that increasing controller order beyond that of a filtered PID, resulted in only marginal performance gains, and further improvements were prevented by the interpatient variability.

The objective used in the current comparison was to minimise the $\mathcal{H}_2$ norm of the measured DoH response resulting from the disturbance model. To introduce further

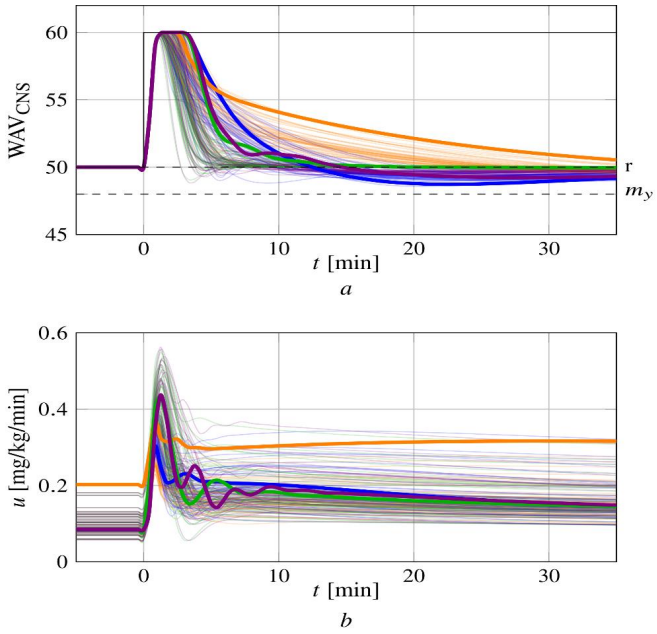

Figure 8. Closed-loop response of the nonlinear patient models when applying a simulated surgical stimulation. *a*) shows simulated Neurosense monitor response. Disturbance is shown in solid black; the dashed black line represents the setpoint r = 50, and the undershoot constraint level m_y imposed. *b*) shows the corresponding infusion profiles *u*. Thick lines show the highest cost over the patient model set for each considered controller type. Colours according to Table 1.

robustness and associated conservatism, an uncertainty description from the model set was generated and considered for the synthesis of a robust controller as proposed in [16]. This approach enables the use of model-based designs, from a small number of models with significant spread in frequency response. Since a set of models was considered here, worst-case performance over the model set was optimised, while ensuring that each imposed constraint was fulfilled for each model of the set. While optimising mean or median performance constitutes possible alternatives, the worst case was chosen here since it introduces safety through conservatism.

Disturbance attenuation was balanced against undershoot, through imposing a constraint of 10 WAV_{CNS} on the latter. Relatedly, a trade-off between performance and control signal activity was introduced through constraining the noise sensitivity function. It could be noted that the

associated constraint levels $M_s = 2.55$ and $M_t = 2.08$ exceeded the typical recommendation [21]. The reason is that robustness to interpatient variability was enforced to a large degree by taking the model set into account, as opposed to designing for a single patient model and enforcing robustness across the set using the mentioned constraint levels. Here, *Ms* and *Mt* should instead be viewed as providing additional robustness, ensuring stability for patient models which were not fully represented by those in $\mathcal{P}$.

While the presented comparisons have provided no indications that the main results would differ with other clinically representative models or synthesis problem formulations, a careful choice of the latter is important to ensure clinical relevance. There exist applications where a slightly differing objective could be preferable. In [23], a PID controller for propofol anaesthesia was optimised and clinically evaluated. Limiting the time of induction for anaesthesia was more heavily emphasized, resulting in parameters values differing slightly from the ones reported here. In addition, a comparison between a PID controller and a higher-order model-based controller was conducted in [30]. However, both controllers included in the comparison were manually tuned. Although the same design objective was considered for both controllers, different design criteria were implemented.

The main limitation of our study lies in the infeasibility of finding the optimal Youla parameter for a set of models. While unknown, its performance would be upper bounded by K_Q and lower bounded by K_{set}. This is why we have compared optimal Youla parameters for individual patient models to corresponding optimal filtered PID controller. The two rightmost boxes of Figure 3 reveal that there is very little difference in performance between these two designs. Separate comparison between the individualized filtered PID controllers (K_{ind}), and those designed to be perform robustly across the interpatient variability (K_{set}, K_Δ) reveals that the main performance difference between designs included in the study can instead be attributed to the interpatient variability.

6. Conclusion

Given clinically imposed requirements on robustness in combination with representative interpatient variability, increasing controller order beyond that of a filtered PID controller does

not significantly increase achievable performance in propofol DoH control. Relatedly, there is a significant discrepancy between the achievable performance when considering an individual patient model compared to a model capturing representative variability within a target population. To conclude, there is little to gain by increasing controller complexity, unless model uncertainty stemming from interpatient variability is reduced.

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Appendix

Expressions pertaining to the studied optimisation problem are derived below. The optimisation objective of (7) is to minimise the (squared) $\mathcal{H}_2$ norm of the output, resulting from a load step disturbance:

$$\min_{K} \max_{P_\Delta} \left\| S_\Delta \frac{1}{i\omega} \right\|_2^2 = \min_{K} \max_{P_\Delta} \frac{1}{\pi} \int_0^\infty \left| S_\Delta \frac{1}{i\omega} \right|^2 d\omega, \qquad (A.1)$$

where

$$S_\Delta = \frac{1}{1 + P_0 KM + |KM|\rho\Delta} \qquad (A.2)$$

is the uncertain sensitivity function generated by P_Δ. Introducing

$$\bar{S} = \max_{P_\Delta} |S_\Delta|,$$

the minimisation of (A.1) can be formulated as

$$\min_K \frac{1}{\pi}\int_0^\infty |S_\Delta|^2 \frac{1}{\omega^2} d\omega = \min_K \frac{1}{\pi}\int_0^\infty \bar{S}^2 \frac{1}{\omega^2} d\omega.$$

The expression (8) for $\bar{S}$ is obtained by taking the modulus of (A.2). Let φ be the argument of the term $1 + P_0KM$ in the denominator of (A.2). Maximisation of (8) under $\rho\Delta$ then occurs for a point on the boundary of Δ with argument $-\varphi$. The modulus of S_Δ at this point is given by (8).

In the absence of uncertainty, $\mathcal{H}_\infty$ constraints on S and T are equivalent to the loop transfer function, L avoiding discs in the Nyquist plane for all considered frequencies:

$$|L - c| - r \geq 0. \qquad \text{(A.3)}$$

The centres c_* and radii r_* of these discs are

$$c_s = -1, \quad r_s = \frac{1}{M_s}, \quad c_t = -\frac{M_t^2}{M_t^2 - 1}, \quad r_t = \frac{M_t}{M_t^2 - 1},$$

where the subscripts s and t correspond to the sensitivity and complementary sensitivity constraints, respectively. See, [31] for further details. Generalisations to the case involving the additive uncertainty $\rho\Delta$, comprises maximising (A.3) under P_Δ. The methodology is the same as used to obtain the expression (8) from (A.2), resulting in

$$|P_0KM + 1| - \rho|KM| - \frac{1}{M_s} \geq 0$$

$$\left|P_0KM + \frac{M_t^2}{M_t^2 - 1}\right| - \rho|KM| - \frac{M_t}{M_t^2 - 1} \geq 0.$$

The (squared) $\mathcal{H}_2$ constraint on noise sensitivity can be expressed as

$$\max_{r\Delta} \frac{1}{\pi}\int_0^\infty |K|^2|S_\Delta|^2 d\omega \le M_{ks}^2$$

$$\Leftrightarrow \frac{1}{\pi}\int_0^\infty |K|^2\bar{S}^2 d\omega \le M_{ks}^2.$$

The undershoot constraint $y \ge m_y$ is enforced point-wise in the step response. This is achieved by constraining

$$\underline{y_k} = \min_{P_\Delta} \mathcal{F}^{-1}\left(S_\Delta \frac{1}{i\omega}\right), \tag{A.4}$$

where $\underline{y_k}$ is the minimum of the response y under P_Δ at sample k and $\mathcal{F}^{-1}$ the inverse Fourier operator. The minimum $\underline{y_k}$ of (A.4) can be expressed as

$$\underline{y_k} = y_{k,0} - \frac{1}{N}\sum_{n=0}^{N-1} \bar{\rho}_n, \tag{A.5}$$

where $y_{k,0}$ is the inverse Fourier transform of the response with the nominal model P_0 in the loop. For each frequency grid point, indexed by n in (A.5), the worst case contribution $\bar{\rho}_n$ can be obtained similarly to how $\bar{S}$ was obtained from S_Δ:

$$\bar{\rho}_n = \frac{|KM|\rho}{|1 + P_0 KM|^2 - |KM|^2\rho^2}\frac{1}{2\pi\omega_n}. \tag{A.6}$$

Like before, the angular frequency argument (here ω_n) has been dropped from (A.6), to facilitate readability.

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Research items

The research works co-authored by the PhD student are listed below. They have been grouped according to the type of publication.

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1. *Machine learning techniques for computer-based decision systems in the operating theatre: application to analgesia delivery.* Gonzalez-Cava, Jose M.; Arnay, Rafael; León, Ana; Martín, María; Mendez-Perez, Juan A.; Reboso, Jose A.; Jove-Perez, Esteban; Calvo-Rolle, Jose L. Logic Journal of the IGPL. 2020. https://doi.org/10.1093/jigpal/jzaa049.
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