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PID control of depth of hypnosis in anesthesia for propofol and remifentanil coadministration

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Nada conseguiremos na vida sem trabalho.
We can achieve nothing in life without work.

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Abstract

The purpose of general anesthesia is to deeply sedate a person so that they lose consciousness, sensitivity, and body reflexes, and so that surgeries can be safely performed without the patient feeling pain or discomfort during the procedure. General anesthesia is a combination of the effect of three components, namely hypnosis, analgesia, and neuromuscular blockade. Each component is regulated through the action of a specific drug, or through the combined effect of two or more drugs.

In recent years there have been many advances in the field of automatic control systems for drug delivery during anesthesia, which can be implemented using a wide variety of controllers and process variables. The reason behind these advances is that an automatic control system can provide several benefits, such as a reduction in the anesthesiologist's workload, a reduction in the amount of medication used (which implies a faster and better recovery time for the patient in the postoperative phase), and, in fact, a more robust performance with fewer episodes of over- or under-dosing of the drug.

A proportional-integral-derivative controller (PID) continuously calculates the error value that is the difference between the desired value and the measured process variable and applies a correction that is based on proportional, integral and derivative terms. In this dissertation, a specific PID control system for propofol and remifentanil is proposed to regulate the hypnosis component during anesthesia using the bispectral index (BIS) as the process variable. Infusion rates of both drugs are also controlled. The adjustment of the PID parameters, so that the BIS was closer to what was expected, was done using a genetic algorithm.

The implementation of the control system was done in Simulink in order to simulate a surgery. The simulation scheme includes the patient models for both drugs, a disturbance profile, and two different PID controllers for the two phases of anesthesia - induction and maintenance. Aspects such as noise in the BIS signal and artifacts were taken into account in the system and a suitable noise filter was applied in the control algorithm. In addition, a ratio between the infusion rates of propofol and remifentanil has been introduced to allow the anesthesiologist to choose the appropriate opioid-hypnotic balance

In the end, a performance analysis of the control system was made based on seven performance indices (namely the integrated absolute error, the settling time, the median performance error, the median absolute performance error, the wobble, and the above and below recommended BIS values).

Although there are many types of control systems for the automatic control of hypnosis depth described in the literature, these are not usually used in clinical practice. Therefore, it is important to continue research to produce robust and user-friendly systems that integrate clinicians' clinical knowledge and meet their actual needs.

Keywords: genetic algorithm, BIS, PID, propofol, remifentanil, Simulink.

Resumo

A anestesia geral tem como objetivo sedar uma pessoa profundamente, de forma a que perca a consciência, a sensibilidade e os reflexos do corpo e, assim que as cirurgias possam ser realizadas de um modo seguro sem que o paciente sinta dor ou desconforto no decorrer do procedimento. A anestesia geral é uma combinação do efeito de três componentes, nomeadamente a hipnose, a analgesia e o bloqueio neuromuscular. Cada componente é regulada através da ação de um medicamento específico, ou através do efeito combinado de dois ou mais medicamentos.

Caso a anestesia geral seja total intravenosa, o medicamento anestésico é injetado diretamente na veia sem recurso a agentes de inalação, causando uma sedação quase imediata. A profundidade da hipnose depende do tipo e da quantidade de medicamento injetado pelo médico, que também irá depender da duração da cirurgia, da sensibilidade de cada pessoa e de outros parâmetros como a idade, o peso, a altura e condições de saúde.

É de salientar que globalmente, são realizadas 310 milhões de cirurgias importantes por ano, cerca de 40 a 50 milhões nos Estados Unidos da América e 20 milhões na Europa. Como tal, a utilização de um sistema de controlo automático pode proporcionar diversos benefícios, tais como uma redução da carga de trabalho do anestesiologista (que tem, em qualquer caso, de estar presente em cada cirurgia com um papel de supervisão), uma redução da quantidade de medicamento utilizado (o que implica um tempo de recuperação mais rápido e melhor do paciente na fase pós-operatória) e, efetivamente, um desempenho mais robusto com menos episódios de excesso ou défice da dose de fármaco.

Nos últimos anos tem havido muitos avanços no campo dos sistemas de controlo automático para a administração de fármacos durante a anestesia, que podem ser implementados através do uso de uma grande variedade de controladores e variáveis de processo. Nesta dissertação, é proposto um sistema de controlo PID específico para o propofol e remifentanil, de modo a regular a componente da hipnose durante a anestesia, utilizando o índice bispectral (BIS) como a variável de processo. O objetivo era manter o valor do BIS próximo do valor de referência desejado durante a maior parte da simulação. Um valor BIS entre 40 e 60 sugere um nível adequado de anestesia geral. Portanto, o valor de referência escolhido para o BIS foi 50. As concentrações de ambos os fármacos também são controladas.

Um controlador PID calcula de forma contínua fo valor de erro que é a diferença entre o valor desejado e a variável de processo medida e aplica uma correção que tem por base os termos proporcionais, integrais e derivativos (denominados P, I, e D respetivamente), daí o nome. Neste trabalho realizou-se o ajuste dos parâmetros PID de modo a que o BIS estivesse mais próximo do que era esperado (BIS=50). Sendo que o ajuste foi feito usando um algoritmo genético. O algoritmo genético é conhecido por ser um método estocástico de busca global que replica o processo de evolução ou seja, o algoritmo baseia-se de forma resumida num processo iterativo de seleção, recombinação, mutação e avaliação. Neste trabalho, o tempo máximo estabelecido para o algoritmo genético foi de 1000 segundos.

De modo a incorporar todas as características da anestesia foi necessário usar um modelo matemático. Como tal, foi utilizado um modelo que é dividido no modelo farmacocinético, que se refere à infusão, distribuição e eliminação de um medicamento no corpo e no modelo farmacodinâmico, que descreve a relação entre a concentração de um medicamento no local de efeito e o seu efeito clínico.

A implementação do sistema de controlo foi feita no Simulink de formar a simular uma cirurgia e obter uma melhor visualização. O esquema de simulação inclui os modelos do paciente para ambos os fármacos, um perfil de perturbação e dois controladores PID diferentes para as duas fases da anestesia – a indução e a manutenção. A transição entre uma fase e outra deu-se após os 10 minutos. O perfil de perturbação usado baseia-se num perfil de tempo de compensação BIS que imita um perfil de estimulação cirúrgica geral de 70 minutos que inclui cada passo típico na maioria dos procedimentos cirúrgicos, como a intubação, a incisão cirúrgica, o estímulo abruto, estímulos grandes mas de curta

duração e o fecho. Aspetos como o ruído no sinal BIS e artefactos, foram tidos em conta no sistema e foi aplicado um filtro de ruído adequado ao algoritmo de controlo.

Dois blocos de saturação foram implementados de modo a limitar os valores das taxas de infusão entre 0 e 6,67 mg/s para o propofol e entre 0 μg/s e 16.67 μg/s para o remifentanil. Além disso, foi introduzido um rácio entre as taxas de infusão de propofol e remifentanil cujo o objetivo seria permitir ao anestesiologista escolher o equilíbrio opiáceo-hipnótico adequado. O valor do rácio pode ser escolhido entre 0,5 e 15. A escolha depende se o anestesiologista prefere um componente hipnótico mais predominante em casos de estimulação pouco dolorosa ou de uso concomitante de analgésicos loco-regionais; ou se o anestesiologista prefere um componente analgésico mais predominante em casos de fases cirúrgicas que envolvam uma estimulação forte e dolorosa. Para este trabalho, foi utilizado um rácio de 0,5.

O grupo de pacientes é constituído por 12 pessoas (3 do sexo masculino e 9 do sexo feminino) com idades entre os 28 e os 50 anos de idade. Foi feita uma divisão de acordo com o género, sendo que os parâmetros e os gráficos obtidos são uma média para mulheres e homens. Porém, o sistema pode ser ajustado para só um paciente, daí também ter sido mostrado o gráfico do BIS e os valores dos parâmetros obtidos através do algoritmo genético para um dos pacientes do sexo masculino.

No fim, foi feita uma análise do desempenho do sistema de controlo com base em sete índices de desempenho (nomeadamente o integral do erro absoluto, o tempo de estabilização, o erro médio de desempenho, erro médio absoluto de desempenho, a oscilação, e os valores BIS acima e abaixo dos recomendados). É evidente que o controlador tem um melhor desempenho durante o período de indução, em comparação com a fase de manutenção. Isto é de esperar dado que não são impostas perturbações durante este período, que também é mais curto do que o período de manutenção. É de salientar também o facto de o sistema ser rápido a estabilizar, tendo demorado menos de 4 minutos.

Embora haja muitos tipos de sistemas de controlo para o controlo automático da profundidade da hipnose que tenham sido descritos na literatura, estes normalmente não são utilizados na prática clínica. Por conseguinte, é importante continuar a investigação para produzir sistemas robustos e de fácil utilização que integrem os conhecimentos clínicos dos médicos e vão de encontro às suas necessidades reais.

Algumas sugestões para investigações futuras são sugeridas tais como, incluir variáveis fisiológicas (frequência cardíaca, tensão arterial, saturação de oxigénio no sangue, e concentrações de dióxido de carbono no sangue), fazer a monitorização da analgesia e implementar dois blocos “bolus” (um para cada fármaco) no sistema, para que o médico possa administrar mais doses de fármaco quando necessário.

Além disso, o sistema poderia potencialmente ser aplicado a outros medicamentos para controlar a outra componente da anestesia: o bloqueio neuromuscular. O sistema pode também ser adaptado a crianças.

Os resultados sugerem que o controlo em circuito fechado com o uso do PID pode vir a ser útil, no entanto num trabalho futuro é preciso ter em consideração o tipo de doente, o estado físico e fisiológico, hábitos medicamentosos, tóxicos e etílicos. É de salientar que este sistema não pode ser visto como uma substituição da perícia humana mas como um instrumento de ajuda.

Palavras chave: algoritmo genético, BIS, PID, propofol, remifentanil, Simulink.

Contents

List of figures

List of tables

List of abbreviations

AEP	Auditory evoked potential
BIS	Bispectral
CNS	Central nervous system
DoA	Depth of anesthesia
DOH	Depth of hypnosis
DR	Disturbance rejection
EEG	Electroencephalography
EMG	Electromyography
GA	Genetic algorithm
GABA	Gamma-aminobutyric acid
IAE	Integrated absolute error
IMC	Internal Model Control
LoU	Levels of unconsciousness
MDAPE	Median absolute performance error
MDPE	Median performance error
MLAEP	Midlatency auditory evoked potentials
MPC	Model predictive control
NMBA	Neuromuscular blocking agent
PID	Proportional–integral–derivative
RL	Reinforcement learning
SPF	Set-point following
TCI	Target-controlled infusion
TIVA	Total intravenous anesthesia
TR	Tracking
WAVcns	Wavelet-based for central nervous system

1. Introduction

1.1. Clinical anesthesia

During a surgical procedure, the anesthesiologist's mission is to ensure the patient's safety by monitoring the patient and control the pain and the state of consciousness. This dissertation explores clinical anesthesia automation during surgery. Concerning the implementation of the model, it is crucial to have some basic medical knowledge, which will be briefly detailed.

1.1.1. Functional components and anesthetic drugs

A drug-induced, reversible pharmacological state known as anesthesia is described by three main effects on the patient: hypnosis, analgesia, and areflexia. Each component is connected to a particular class of medication.

Hypnosis

Hypnosis is characterized as the level of unconsciousness necessary to avoid intraoperative awareness and memorization. To induce or maintain general anesthesia, five inhalational anesthetics exist (Nitrous Oxide, Isoflurane, Sevoflurane, Desflurane, and Xenon) and five intravenous anesthetics (Propofol, Etomidate, Ketamine, Methohexital, and Thiopental). Then, midazolam, diazepam, and lorazepam are the three sedative benzodiazepines frequently taken with the ten general anesthetic medications already mentioned. Due to its quick redistribution and metabolism within the body, lack of accumulation in tissues, being a pure hypnotic drug, and its decreased risk of adverse side effects, propofol is the most popular form of the intravenous hypnotic drug.

Propofol is a short-acting general anesthetic agent with a rapid onset of action of approximately 30 to 40 seconds [1]. It works as an agonist at GABA receptors to increase inhibition in the central nervous system. Pyramidal neurons, which convert synaptic inputs into a patterned output of action potentials, often exhibit a balance between excitatory and inhibitory control, and propofol strengthens the inhibitory effects. Additionally, propofol increases inhibition by affecting the thalamus and influences the cortex by reducing excitatory inputs.

The indicator that anesthesiologists and researchers use most frequently to control hypnosis is the bispectral index (BIS).

Analgesia

Analgesia is considered as the absence of pain. The most common analgesic drugs belong to the family of opioids (remifentanil, sufentanil, alfentanil, fentanyl, morphine and, hydro morphine), which do not have hypnotic effects at levels appropriate for clinical anesthesia. However, there is a synergistic interaction between opioids and several hypnotic drugs, such as propofol.

Regarding their function, opioids bind to specific CNS receptors and, to a much lesser extent, peripheral tissues outside the CNS, acting as agonists. They primarily work by inhibiting neurotransmitter release, which has a significant analgesic impact.

In the context of closed-loop controlled anesthesia, remifentanil is a good choice because it has very fast redistribution and metabolism[1], it is the fastest-acting of the opioids, and its dynamics are an order of magnitude quicker than those of propofol.

Unlike hypnosis, no accurate pain assessment tool has yet been introduced into clinical practice since there are no proven objective indexes of nociception.

Areflexia

Areflexia is the term used when the muscles do not react to stimuli. The goal is to achieve a level of paralysis that is sufficient for carrying out surgical procedures by using neuromuscular blocking agents (NMBAs). During anesthesia, NMBAs are typically used to facilitate endotracheal intubation and enhance surgical conditions.

By stopping the transmission of nerve impulses, neuromuscular blocking drugs work locally at the neuromuscular junction. Some examples are suxamethonium (succinylcholine), pancuronium, atracurium, vecuronium, and rocuronium. These drugs[2] do not have analgesic and hypnotic properties.

Neuromuscular blockage monitoring is based on electrically stimulating a motor neuron and measuring the induced muscle activity. Typically, electrodes are positioned above the ulnar nerve at the wrist over cleansed skin. Spontaneous breathing and changes in vital signs are additional monitoring measures.

1.1.2. Temporal phases of anesthesia

In a standard surgery procedure, anesthesia can be divided into three temporal phases: induction, maintenance, and emergence. During the induction phase, which is the first stage of anesthesia, the anesthetic variables are adjusted from their initial levels to their target values. Regularly, induction is conducted by giving bolus doses (single high dosage) of propofol and remifentanil, followed by infusions of the two drugs at constant rates.

Once the requisite levels of the anesthetic variables are reached, the maintenance phase begins, during which the surgical procedures are carried out. Despite the presence of disturbances, often brought on by unpleasant stimuli, it is crucial to maintain a sufficient level of hypnosis. The emergency phase is the last stage of anesthesia when the administration of the drugs is interrupted. After 8–10 minutes, the patient begins to regain consciousness.

1.2. Drug dosing regimens

Total intravenous anesthesia (TIVA) is used to deliver all anesthetic drugs intravenously. TIVA can be done by using an initial bolus followed by a continuous infusion at a predetermined rate. From a control perspective, TIVA can be administered using the following dosage regimens: manual control, open-loop feed-forward control, or closed-loop control.

[1] Other opioids are degraded via hepatic biotransformation and renal excretion, while remifentanil is metabolized by esterases in the blood plasma.

[2] Caution should be taken in patients taking the neuromuscular blocking drugs, atracurium, and mivacurium. It is recommended that they should not be administered in the same intravenous (IV) route before the presence of propofol is eliminated.

1.2.1. Manual control

Manual control consists of setting each drug's flow rates into the infusion pumps. The anesthesiologist may also provide bolus dosages via the pump interface if the patient's hypnotic or analgesic condition appears insufficient.

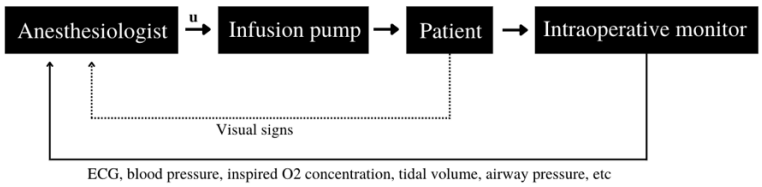

Figure 1.1: Manual control. Schematic adapted from [2]

1.2.2. Open-loop control

Open-loop control is also known as a target-controlled infusion (TCI) system, which is essentially an infusion pump interfaced with a computer.

In this case, the anesthesiologist chooses a target drug concentration rather than an infusion rate. This is either a blood plasma or effect site drug concentration, depending on the TCI system.

Initially, the doctor only needs to enter the patient's age, body weight, height, and sex, as well as the target concentration of the administered drug. The TCI system runs pharmacokinetic simulations (using a patient model) and uses algorithms that periodically calculate or predict the concentration of the drug in plasma and match it with the desired target concentration. If there is a discrepancy, the pump's infusion rate is adjusted.

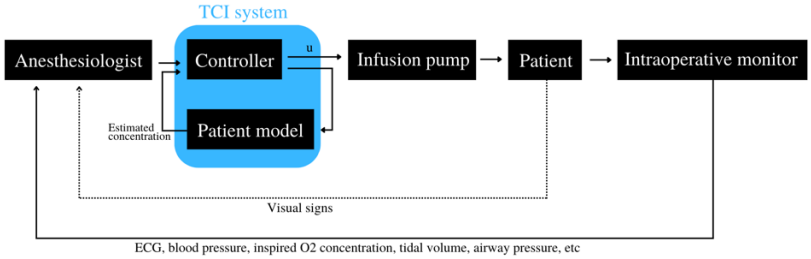

Figure 1.2: Open-loop control. Schematic adapted from [2].

1.2.3. Closed-loop control

In closed-loop control, the system output (a controlled variable) is measured and compared to the desired target value (a set-point), and the difference is utilized to calculate the value of the system input. Often the BIS index, which is based on EEG measurements (this will be explained in the following chapter), is used as the control variable.

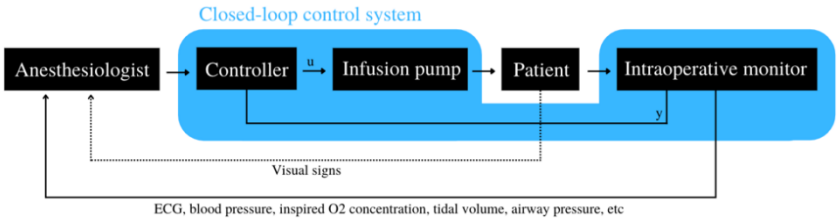

Figure 1.3: Closed-loop control. Schematic adapted from [2].

2. State-of-the-art

Anesthesia controllers to improve clinical training

Control systems would be an asset because they would reduce: (i) the risk of under-and over-dosing, (ii) the doctor's workload, and (iii) the amount of drug used. One of the proposed and mentioned suggestions in several articles [3]–[9] is to use a closed-loop controller. This mechanism allows the automatic regulation of the process variable until it reaches a set, and it has the potential to reduce the effect of inter-patient variability.

In order to build a closed-loop control system that controls the depth of anesthesia (DoA), a control variable is always needed. So this chapter is divided into: 2.1) the control variables that can be measured to ensure the DoA and 2.2) the most diverse types of controllers.

2.1. Control Variables

A control variable, which can be extracted from an electroencephalogram, is a variable that can be measured during a medical procedure or throughout an experiment. Its value is then compared with the initially stipulated target value.

2.1.1. Bispectral index

Although a variety of control variables have been proposed in the literature, the BIS index is the most used index because it correlates well with the concentration of numerous anesthetic drugs in blood and the depth of sedation. The BIS combines information on the frequency, power, and harmonic and phase relationships between the component waves of the EEG. EEG signals are sent from a sensor placed on the patient’s forehead to a digital signal converter, which then transmits the data to a monitor for processing and analysis. An algorithm whose computation is not public knowledge uses a predetermined weighting scheme to convert certain features of the spectrogram, the bispectrum, and the level of burst suppression measured into the index value [10].

The BIS is scaled between 0 and 100, where 0 corresponds to the isoelectric EEG known as a deep coma (when all cortical activity is fully suppressed) and 100 to the awake state where the patient responds to a normal voice. The range between 40 and 60 is considered to be the most widely used in the literature and clinical practice for procedures that require anesthesia.

In [11], it was shown that the BIS monitor could help guide physicians in titrating propofol to adequate sedation for children undergoing painful medical procedures, as well as bone marrow aspiration and biopsy, lumbar puncture, esophagogastroduodenoscopy, colonoscopy, and renal biopsy. In this case, a BIS score of 45 was determined to provide sedation for 95% of the population.

Furthermore, in [9] the target BIS value was 50 after a co-administration of propofol and remifentanil for postoperative sedation in adult cardiac surgery patients.

One major disadvantage of the algorithm mentioned above is that it may present discontinuities from the switching between different analysis modes during transitory events, leading to nonlinear behavior.

2.1.2. Auditory evoked potential (AEP) index

The auditory-evoked potential index is another EEG-derived parameter that can be extracted from the analysis of auditory evoked potentials (AEP). AEP are the electrical potentials evoked in the auditory pathway given sound stimuli, and midlatency auditory evoked potentials (MLAEP) are the EEG response 10–50ms after.

With the administration of anesthetics, AEP amplitudes and latencies change, more specifically, peak amplitudes decrease as their latencies increase, which leads to a decrease in AEP index at the loss of consciousness. The AEP index is calculated from the amplitude difference between consecutive segments of the AEP curves.

An index derived from MLAEPs could be a substitute for BIS. In fact, MLAEP have a faster response than the BIS during propofol-drug induced sleep endoscopy procedure [12]. When monitoring the depth of sedation using propofol or midazolam during the epidural block, the auditory evoked potentials index was considered more valuable [13].

Additionally, in [14], the results suggest the AEP index might be more helpful than BIS during the anesthetic induction of ketamine with propofol because the AEP index values decreased proportionally at the time of loss of response, which did not happen with BIS, i.e., BIS did not decrease.

There are conflicting views in the literature. Some studies show that BIS is better than AEP due to better discrimination between awake and unconsciousness states (for propofol and remifentanil [15], or propofol and alfentanil [16]).

Also, from [16], it can be confirmed that BIS correlates better with the level of sedation than with any of the MLAEP parameters.

2.1.3. The somatosensory evoked potentials (SSEPs)

The somatosensory evoked potentials (SSEPs) monitor the integrity of sensory pathways from peripheral nerves to the sensory cortex by applying an electrical stimulus of 0.2–2ms duration [17] in the median nerve at the wrist, in the peroneal nerve at the knee, or in the posterior tibial nerve at the ankle. The rate of stimulation recommended ranges from 2 to 4 Hz [17] or 5 Hz [18].

SSEPs monitoring has been used during several operations such as carotid endarterectomy (CEA) [19] intracranial aneurysm surgery [20], thoracoabdominal aortic aneurysm repair [21], spine and spinal cord procedures [22] but also during chronic pain management [23].

Body temperature and control cardiorespiratory status should be measured and controlled to detect the changes that hypothermia, the cooling of the stimulated extremities, hypoxia, hypercapnia, hypotension can have in intraoperative SEP monitoring. However, the effects of anesthetics on SEPs must always be considered when interpreting changes in SEPs because these changes are inevitable.

Some advantages of this method are its high sensitivity (0.063% false negatives) and negative predictive value (99.93%) and the fact that the anesthetic effects are relatively well understood, and they can use neuromuscular blockade. Conversely, it requires time-consuming averaging of signals, it monitors only the dorsal columns compromising other parallel sensory pathways, it is sensitive to electrical noise, and it does not record in the presence of peripheral neuropathies [24].

2.1.4. The wavelet-based (WAVcns) index for central nervous system

The wavelet-based index is related to cortical activity, and it is comprised of wavelet analysis of normalized EEG signal in the gamma frequency band (32-64 Hz), which can characterize changes in both time and frequency.

WAVcns index, similarly to BIS, is a numerical index ranging from 0 to 100, with 40–60 representing the interval of values aimed for the hypnotic state.

In 2001, a research group at the University of British Columbia found that the wavelet information can be represented by a probability density function (PDF) [25], making a comparison of the PDF of the cortical state that needs to be determined with two reference PDFs that correspond to the awake and isoelectric part.

Both BIS and WAVcns indices are very similar in steady state periods [26], [27]. Nevertheless, WAV reacts faster during transients (induction, surgical reaction, propofol boluses, and emergence), and it regains its preinduction baseline value (90-100) after emergence from anesthesia.

2.1.5. Entropy

Based on the data acquisition of electroencephalograph (EEG) and frontal electromyograph (FEMG) signals, entropy is another valuable parameter to assess the depth of anesthesia. EEG patterns change from irregular to more regular as general anesthesia progresses. Similarly, FEMG becomes lower as anesthesia gradually reaches deeper brain regions. Two variables of interest are state entropy (SE) and response entropy (RE). The first variable corresponds to the signal's entropy in the 0.8 to 32 Hz band. The second variable corresponds to the entropy of the signal between 0.8 to 47 Hz. The RE is expressed in the 0-100 scale, and the SE scale ranges from 0 to 91. Similarly to BIS, the target range for entropy values is 40-60. The RE is based on both FEMG and EEG recordings, and it shows how the patient reacts to external stimuli and may indicate an early awakening. To evaluate the hypnotic impact of anesthetic drugs on the brain, the SE, a reliable parameter based on EEG, may be utilized. Data is acquired by attaching the Entropy sensor to the patient's forehead.

A study by Balci et al. [28] that used propofol and fentanyl sedation in patients undergoing hand surgery concluded that entropy monitoring is as sensitive as BIS. The same conclusion was drawn from the research in [29], using propofol, thiopental, sevoflurane, and desflurane.

Also, in [30], entropy was considered a trustworthy indicator to assess DoA for laryngeal mask airway insertion during sevoflurane and propofol infusion.

2.1.6. Power spectrum

Median frequency (MEF) and spectral edge frequency (SEF) are the most common parameters based on Fourier analysis to characterize the spectral analysis. The MEF is the frequency that divides the power spectrum distribution into two parts of identical power. MEF is expected to decrease as the depth of anesthesia increases. The SEF is the frequency up to which 95% of the EEG power is present. One advantage of the SEF is its high sensitivity to deepening hypnotic levels [31]. These parameters come from EEG and they are acquired by placing electrodes on the following areas of the skull: fronto-polar, frontal, central, temporal, parietal, and occipital areas.

Power spectrum techniques may be questionable because of the variable effects of different anesthetic agents and the large inter-patient variability observed due to ignoring the inter-frequency phase information in the EEG.

Due to these facts, new EEG indices – such as the bispectral index, approximate entropy, auditory evoked potentials, or somatosensory evoked potentials – have gained more popularity.

In 1998, Gajraj et al. [31] compared the AEP index, power spectrum, and the BIS index during transitions from consciousness to unconsciousness produced by target-controlled infusions of propofol for patients undergoing hip or knee replacement. A threshold value with a specificity of 100% for a state of unconsciousness was defined. More precisely, 37 for the AEP index (52% sensitivity), 55 for BIS

(15% sensitivity), and 16 for SEF (9% sensitivity). There was no recorded value for MF that was 100% specific for unconsciousness. It was found that the auditory evoked potential was the best indicator of loss of consciousness, followed by BIS with SEF being the least efficient.

Even though the power spectrum may not have been considered the control variable in the latest studies, its analysis still provides valuable information during intraoperative monitoring.

2.2. Controllers

2.2.1. Proportional-integral-derivative (PID)

Regarding the PID controller, the proportional term determines the required action depending on the current error, the integral term determines the required action characterized by the sum of current and past errors, and the derivative term determines the required action regarding the rate at which the controlled variable is changing.

Because of fewer side effects, most of the PID controllers are used during coadministration of propofol [3], using a control loop feedback mechanism in which the BIS level is used as a feedback parameter to control the depth of hypnosis. In recent studies, PID was used for propofol together with remifentanil [5], [6]. Since the concentrations of propofol and remifentanil needed are different, the target ratio for different surgeries could be selected by the anesthesiologist.

The Wiener model can be used to describe the relationship between propofol and remifentanil infusions and the BIS value. First, the PID controller is implemented by a series connection of a pharmacokinetic-pharmacodynamic (PK/PD) model and a nonlinear Hill function. If both propofol and remifentanil are used, the two decoupled linear PK/PD models are represented in parallel [6] [5]. The Hill function describes the relationship between the effect site concentration and the BIS index, while the PK/PD model describes the relationship between propofol infusion rate and the effect site concentration.

The PK/PD model can be described using a three-compartment mamillary model, assuming that each compartment has homogeneous mixing properties. This method, which is later presented in Figure 3.1, divides the body into compartments and measures the number of drugs transferred between them. In the PK/PD model from [3], a drug is given in the central compartment V1 and is then distributed to V2 and V3. The central compartment, V1, is a plasma compartment in which drugs dissolve and are delivered to the other compartments. The second compartment, V2, is a shallow peripheral compartment characterized by rapid drug diffusion from the plasma to this compartment. The third compartment, V3, is a deep peripheral compartment with a slow drug delivery rate (due to the equilibrium between the blood and the tissues) from V1 to this compartment. The drug transfer rate from one compartment to another and the elimination rate of the drug are also included. Moreover, to offset the time lag between the observed effect and the plasma concentration, an additional compartment that links the plasma concentration to the effect concentration is inserted. The model is described by a first-order derivative system and the Schnider's model is used to calculate the parameters of the model for propofol. When using propofol and remifentanil, the parameters of the model for remifentanil are calculated using the Minto's model. Both models take the following into account: the patient's height, weight, age, and gender.

Secondly, an anti-windup strategy is implemented by using the conditional integration technique to decrease the negative effect of saturations on the PID, even though it is not required for the provided tunning.

Finally, a genetic algorithm to optimize the controller parameters was used. Also, in [3], a noise filter was added to the algorithm because of noisy BIS signal and artifacts, and a gain scheduling strategy was implemented to take care of induction and maintenance phases separately (based in [4]). In [6] and [5], after having a PK/PD model with some pre-defined values for the nonlinear model for propofol with remifentanil, the Particle Swarm Optimization (PSO) algorithm was used instead of the genetic algorithm used in [3] for only propofol. PSO simulates the disturbance rejection response giving the set of optimal PID parameters that reduces the integral absolute error for that specific patient.

2.2.2. Fuzzy Logic

Fuzzy logic, an impressive mechanism that can imitate the decisions of anesthetists, can also be used for controlling and monitoring DoA. Fuzzy control algorithm consists in the fuzzification, fuzzy reasoning and defuzzification.

In fuzzification, the membership functions and their ranges are defined for all input and output variables. In fuzzy reasoning, known as inference, the degree of truth of the various rules of the system is calculated, and the output value is associated with each rule. These rules are generally derived from a knowledge base derived from human expertise, and it is of the type: IF input 1=A and input 2=B, THEN output=C, where A and B are input membership functions and C is the output membership function. *Mamdani* and *Sugeno's* fuzzy inferences are the most widely used inference methods. Since the value of the calculated output is fuzzy, a defuzzification technique is used to obtain a numerical value for the output consistent with the rule base and generalization presented by the fuzzy logic framework. Defuzzification can be achieved in several ways, but the most common is the centroid method also called center of area (COA) or center of gravity [32].

The study of fuzzy logic control theory is currently growing at a very fast pace. In [33], a fuzzy controller was implemented during surgery under propofol anesthesia using four parameters as inputs: blood pressure, heart rate, age and weight. Then, the information was processed, and the DoA was obtained as output. It was concluded that age and weight were the most relevant, and it was shown how the doses of the anesthesia were very related to these parameters.

In [34], the inputs to the fuzzy inference system were BIS error, and BIS rate, and the output was the infusion rate increment. The fuzzy logic based closed-loop system was tested to automate propofol administration in 42 patients scheduled for ambulatory surgery (gynecological, vascular, and general surgery) with a BIS target of 50.

Also, in [35], a fuzzy logic system for risk evaluation of 218 consecutive patients undergoing laparoscopic cholecystectomy operations was presented. Five major criteria including pulmonary chronic obstructive pulmonary disease, cardiac coronary artery disease and congestive heart failure, renal chronic kidney disease, liver disease and diabetes mellitus and three minor criteria, including age, cigarette smoking, and BMI were considered the inputs of the method. The output was the risk percentage. Even though the purpose of this paper is not to monitor and control hypnosis, the proposed fuzzy logic system also provides significant benefits, such as avoiding unnecessary utilization of intensive care units, reducing hospitalization times, and decreasing patient care expenses.

2.2.3. Internal Model Control (IMC)

Internal model control systems are characterized by a controller device that contains the process and the process model known as the internal model, which is a simulation of the process.

In the IMC proposed in [36], an approximate linear PK-PD model was used to regulate each patient's BIS. The internal loop model calculates the difference between the outputs of the process and the internal

model, showing the effect of disturbances and a mismatch in the model. Also, it is frequently implemented in series with a low-pass filter, as the inverse of the process model, in order to mitigate the effects of process and model inconsistencies at the high-frequency end of the system's frequency response. In the process part, the anesthetic drug concentration and the plasma concentration are the input and output of the PK model, respectively, and the plasma concentration and effect-compartment concentration are the input and output of the PD model, respectively.

The IMC controller has been proven to be more robust to intra- and inter-patient variability, as well as disturbances and measurement noise. Notwithstanding, it has the drawback of being unable to handle open-loop unstable systems, and nonlinear models must be linearized before the controller can be designed.

2.2.4. Model predictive control (MPC)

The main goal of the MPC is to predict how to sequence future control moves so that the sequence of predicted responses (output variables) approaches the defined target of the control variable. This method is based on making predictions about the future behavior of the system using a model of the system.

MPC consists of a patient model (PK-PD model) [37], a prediction block, and a controller. Firstly, the patient model is used to predict the value of the output. Then the discrepancy between this value and the one from the model output serves as the prediction block's feedback signal. With this difference and the initial input, the prediction block predicts the future values of the output, and the controller calculates the future input dosage of which only the first input value is implemented by the controller.

Recently, Ntouskas et al [38] proposed a robust MPC based on a linear matrix and a Kalman filter, which is a predictor-corrector algorithm. The Kalman filter uses the current output and current input to estimate the future state (a state vector) of the system in the next time instant which is used as an input by the MPC controller. The controller then calculates the optimal input, which is the administration rate of propofol, which is administered to the patient, and the loop is repeated.

In [37], a comparison between PID, IMC and MPC was completed. The MPC has been determined to be the most effective controller model, and has hence been suggested for controlling DoA during propofol administration. The biggest advantage over other models, is that MPC can prevent input and output constraint violations, drive some output variables to their optimal targets while keeping other outputs within specified ranges, and keep input variables from varying too much.

2.2.5. Fractional

A fractional controller uses fractional calculus with integrals and derivatives of arbitrary orders. Fractional calculus can be used by applying a “Commande Robuste d’Ordre Non Entier” (CRONE) methodology (formulas can be found in [39]). CRONE has the advantage of making the closed-loop system insensitive to gain changes.

In most cases, a third-generation CRONE controller is used due to its ease of handling the most general perturbation model. The CRONE controller was shown to give tighter control of DoA with less oscillation around the set-point, and to more quickly respond to changes in the DoA caused by the noxious stimuli (e.g., laryngoscopy, skin incision, intubation [40]) profile compared to the PID controller [41].

2.2.6. Controllers using machine learning

2.2.6.1. Reinforcement learning (RL) controller

Over the past decade, artificial intelligence has been an object of study in the medical field. More recently, a group of scientists have developed and trained a neural network to calculate the administration of propofol and to control the unconsciousness level of the patients [42] by using reinforcement learning (RL). RL is a subfield of machine learning that analyzes how intelligent agents should behave in a specific environment to maximize the notion of cumulative reward. A typical RL scenario is represented as follows: an agent performs actions in the environment, which are translated into a reward and a representation of the state, which are then sent back to the agent.

In [43], the environment is represented by the PK-PD model with randomized parameters, and it describes how a drug infusion profile generates a series of levels of unconsciousness (LoU). The agent gets a measured LoU from the environment, as well as a target LoU, at each timestep, and calculates how much propofol to administer. Then, the agent generates an observation vector based on the inputs (target LoU and measured LoU) and the infusion history; and the PK model with generic parameterization is used to calculate the estimated effect site concentration. This model is propagated 30 seconds forward at each time under the assumption that there would be no more infusion to give, and the predicted change is computed. All parts of the observation vector are calculated only from prior actions and measured LoUs. Thereafter, the agent utilizes a neural network to map observations to distributions over the action space that is known as the policy.

The propofol dosage task is described as a partially observable Markov decision process (POMDP), which is solved using the cross-entropy method. This method is used to train the agent's policy network. The algorithm runs batches of simulations and adjusts the policy based on the episodes where the agent performed best at the conclusion of each batch. A reward function is used to evaluate the agent's performance in a specific episode providing a flexible framework for rewarding or penalising certain agent activities. Although the model is yet to be tested with real patients, it was concluded that the system outperforms PID controllers.

2.2.6.2. Neural networks

Neural networks are a subset of machine learning that are broadly used in trading and business analytics but lately they have made remarkable progress in the surgical field, more particularly during anesthesia. This method is considered to be the heart of the deep learning algorithms and it consists of a node layer (with an input), one or more hidden layers and an output layer, respectively. Each node is connected to the others, and it has a weight and threshold linked with it. If a node's output exceeds a certain threshold value, the node is activated, and data is sent to the next layer of the network. Otherwise, no data is sent on to the network's next layer. The training data is used by neural networks to learn and increase their accuracy over time.

An example of the application of neural networks is the empirical model that was developed to predict changes in BIS during target-controlled propofol and remifentanil infusions [44]. In order to simulate the PK-PD parts of the model, two neural networks (long short-term memory and the feed-forward neural network) were used. The major advantage of replacing PK-PD over neural networks is the fact that it requires only the dosing history and measured effect instead of blood samplings and drug concentration analysis which cost money and raise some ethical concerns. Also, the covariates (e.g., cardiac output and hemorrhage) that could influence the PK–PD can be easily added to the neural

network's input nodes, and the combined action of more than two medications can be represented by adding additional long short-term memory inputs.

The historical record of infusion of propofol and remifentanil served as inputs to the long short-term memory, whereas the outputs of the long short-term memory and demographic data such as age, sex, weight, and height served as inputs to the feed-forward network. The final output of the feed-forward network was the BIS index. At the beginning of this process, a grid search method was used to optimize the numbers of memory cells and nodes in the neural networks and then a fivefold cross-validation approach was used to test these combinations, selecting at the end the number of memory cells (8) for the long short-term memory and the number of nodes (16) for the feed-forward neural network that would give the smallest validation error. Then the validation error is calculated by applying the trained model to the validation data set, which is the absolute difference between the model predicted BIS and the observed BIS. As the training epoch repeats, the validation errors decrease, and the model is chosen when the validation error is at its lowest.

2.2.7. Positive state observer

A state observer is a system that estimates the internal state of a given real system based on measurements of the real system's input and output more concretely in anesthesiology is based on the amounts of administered drugs and the measurements of the BIS. In [45], a positive state observer was proposed for the automatic administration of propofol and remifentanil in order to keep track of a targeted BIS levels during a surgical procedure.

Firstly, the parameter parsimonious model (PPM) - a new Wiener model - was used to model the effect concentrations of propofol and remifentanil. The PPM can be represented by a state space representation, and it has the advantage of having a reduced number of parameters to be identified.

However, unlike the traditional PK/PD models, most of the state components have no physiological value but the model exhibits a compartmental structure, which has the advantage of allowing the use of the positive control law. The positive control law is a combination of a linear controller with a positivity constraint for the drug doses that ensures tracking of a desired output reference value.

Secondly, an observer was needed because all the state components of the model cannot be measured in practice. This observer is built to estimate the states of the PPM by monitoring the BIS of a real patient and the propofol and remifentanil dosages provided.

Finally, the positive control law was integrated in the Galeno[3] platform which is a program created as part of the Galeno project, by the Portuguese funding agency (FCT), and it includes many identification and control techniques for anesthetic automation. For testing, the control law was used for the automatic administration of propofol and remifentanil to real patients during surgical procedures.

[3] Galeno is now in use in a surgery room at Pedro Hispano Hospital, in Matosinhos, Portugal.

3. Materials and Methods

This section is based on the dataset and schematic implemented in [5] with some adjustments in the disturbance profile. This study differs from [5] since a genetic algorithm was used to adjust the PID parameters. Additionally, the concentration of propofol and remifentanil at the effect site was analyzed.

3.1. Patient model

The most used monitoring measure for showing a patient's state of anesthesia is the BIS index, as described in Section 2.1.1. – this was the control variable used in this work. In order to use the BIS, a mathematical model is required to incorporate all features of anesthesia, including the physiological characteristics and the relationship between the administered anesthetic dose and the effect on the patient in terms of hypnosis and analgesia.

Models can be created using differential equations that are frequently linearized around a system's operational point. The transfer function, which describes the input-output relationships, can then be created from this set of differential equations.

In this dissertation, the adopted patient model is divided into: a) a pharmacokinetic model, which refers to the infusion, distribution and elimination of a drug in the body (PK), and b) a pharmacodynamic (PD) model, which describes the relationship between effect site concentration of a drug and its clinical effect. The drugs used to induce hypnosis and analgesia were propofol and remifentanil, respectively. The two parallel linear systems (one for each drug) are coupled trough a static nonlinear function.

3.1.1. Pharmacokinetic model

A mamillary compartmental model was used to express the relationship between dose and blood plasma concentration for each drug. This system is defined as a combination of connected compartments that are homogeneous and instantaneously well-mixed and that exchange material among them and with the environment. Each compartment represents a tissue group that has similar kinetic characteristics. As shown in Figure 3.1, the body can be divided into three compartments: a small central compartment containing arterial blood and other highly perfused tissues such as the brain, a larger compartment containing muscles, and a third huge compartment including fat tissues and bones.

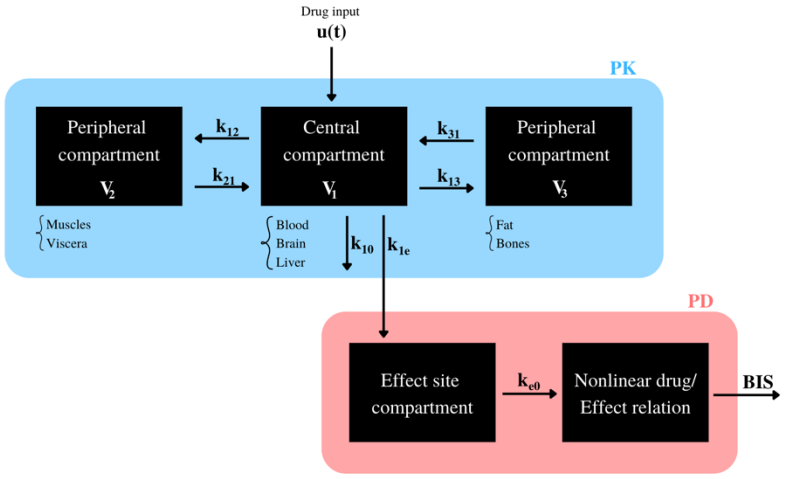

Figure 3.1: Graphical representation of a three-compartmental mammillary model with effect site.

The three-compartment pharmacokinetic model can be expressed as:

$$\dot{q_1}(t) = -(k_{10} + k_{12} + k_{13})q_1(t) + k_{21}q_2(t) + k_{31}q_3(t) + u(t) \quad (3.1)$$

$$\dot{q_2}(t) = k_{12}q_1(t) - k_{21}q_2(t) \quad (3.2)$$

$$\dot{q_3}(t) = k_{13}q_1(t) - k_{31}q_3(t) \quad (3.3)$$

where q(t) is the quantity of drug in each compartment, u(t) is the drug infusion in the central compartment, V_i (i=1, 2, 3) is the volume of the i^{th} compartment and k_{ij} (i,j=0, 1, 2, 3, i≠j) the distribution rate, where i represents the starting compartment and j the ending compartment. The rate constant k_{10} represents the elimination of the drug from the body, from the central compartment. A new compartment (effect site) is added to the model to represent the drug's transit to the site of action. K_{1e} and k_{e0} is the frequency of the drug transition from the central to the effect site compartment and the interaction of the drug elimination from the effect site compartment, respectively ($k_{1e} \approx k_{e0}$ because the effect site compartment can be assumed to be small).

The parameters k_{ij}, V_i and Cl_i (clearance rate) were calculated using the equations from the PK model proposed by Schnider et al [46] for propofol and by Minto et al [47] for remifentanil. The reason behind this choice is because Schnider model is still implemented in most TCI system. Also, in contrast to the Schnider model, the Marsh model does not account for the patient's age. As a result, when considering the Marsh model in elderly patients, the concentrations of propofol in the plasma will actually be higher than expected which may cause hemodynamic instability [48].

The Minto model is applicable to a wide variety of patient characteristics which make it very popular.

For each drug k_{ij} is calculated as follows:

$$k_{10} = \frac{Cl_1}{V_1} \quad [min^{-1}] \quad (3.4)$$

$$k_{12} = \frac{Cl_2}{V_1} \quad [min^{-1}] \quad (3.5)$$

$$k_{21} = \frac{Cl_2}{V_2} \quad [min^{-1}] \quad (3.6)$$

$$k_{13} = \frac{Cl_3}{V_1} \quad [min^{-1}] \quad (3.7)$$

$$k_{31} = \frac{Cl_3}{V_3} \quad [min^{-1}] \quad (3.8)$$

The removal rate of the drug from the body is represented by Cl_1 and from the central compartment to the other two compartments by Cl_2 and Cl_3.

The parameters related with the infusion of propofol [49], [50] are as follows:

$$k_{e0} = k_{1e} = 0.456 \quad [min^{-1}] \quad (3.9)$$

$$V_1 = 4.27 \quad [l] \quad (3.10)$$

$$V_2 = 18.9 - 0.391 \times (age - 53) \quad [l] \quad (3.11)$$

$$V_3 = 238 \quad [l] \quad (3.12)$$

$$C_{l1} = 1.89 + 0.0456 \times (\text{weight} - 77) - 0.0681 + 0.0264 \times (\text{height} - 177) \quad [\text{l/min}] \tag{3.13}$$

$$C_{l2} = 1.29 + 0.024 \times (\text{age} - 53) \quad [\text{l/min}] \tag{3.14}$$

$$C_{l3} = 0.836 \quad [\text{l/min}] \tag{3.15}$$

The parameters related with the infusion of remifentanil [49]

$$k_{e0} = 0.595 - 0.007 \times (\text{age} - 40) \quad [\text{min}^{-1}] \tag{3.16}$$

$$V_1 = 5.1 - 0.0201 \times (\text{age} - 40) + 0.072 \times (\text{LBM} - 55) \quad [\text{l}] \tag{3.17}$$

$$V_2 = 9.82 - 0.0811 \times (\text{age} - 40) + 0.108 \times (\text{LBM} - 55) \quad [\text{l}] \tag{3.18}$$

$$V_3 = 5.42 \quad [\text{l}] \tag{3.19}$$

$$C_{l1} = 2.6 + 0.0162 \times (\text{age} - 40) + 0.0191 \times (\text{LBM} - 55) \quad [\text{l/min}] \tag{3.20}$$

$$C_{l2} = 2.05 - 0.0301 \times (\text{age} - 40) \quad [\text{l/min}] \tag{3.21}$$

$$C_{l3} = 0.836 \quad [\text{l/min}] \tag{3.22}$$

The LBM is calculated using the James formula [51] described below:

$$\text{Males: LBM} = 1.1 \times \text{weight} - 128 \times \left(\frac{\text{weight}}{\text{height}}\right)^2 \tag{3.23}$$

$$\text{Females: LBM} = 1.07 \times \text{weight} - 148 \times \left(\frac{\text{weight}}{\text{height}}\right)^2 \tag{3.24}$$

where weight is expressed in kilogram [kg] and height in centimeter [cm].

3.1.2. Pharmacodynamic model

The PK model's output is the plasmatic concentration of each drug $C_p(t)$, which is also the PD model's input. The PD model relates the plasmatic concentrations $C_p(t)$ to the effect site concentrations $C_e(t)$, resulting in the following formulation of the linear part of the PD model:

$$\dot{C_e}(t) = k_{1e}C_p(t) - k_{e0}C_e(t) \tag{3.25}$$

The static nonlinear function known as the Hill function completes the PD model by mathematically combining the effect site concentrations. The output of the Hill curve is the clinical effect, which in this case is the BIS.

$$\text{BIS}(t) = E_0 - E_{max} \times \left(\frac{\left(\frac{U_{prop}(t)+U_{remif}(t)}{U_{50}(\phi)}\right)^{\gamma}}{1 + \left(\frac{U_{prop}(t) + U_{remif}(t)}{U_{50}(\phi)}\right)^{\gamma}} \right) \tag{3.26}$$

In (3.26), the BIS is a dimensionless index normalized between 0 and 100, $E_0 \approx 100$ and describes the patient state without taking any drug, E_{max} represents the full effect value measured due to the dose rate and γ explains the steepness of the curve (i.e., the receptiveness of the patient to the drug).

$$U_{prop}(t) = \frac{C_{e,p}(t)}{C_{e50,p}} \tag{3.27}$$

$$U_{remif}(t) = \frac{C_{e,r}(t)}{C_{e50,r}} \tag{3.28}$$

$$\phi = \frac{U_{prop}(t)}{U_{prop}(t) + U_{remif}} \tag{3.29}$$

$$U_{50}(\phi) = 1 - \beta \times \phi + \beta \times \phi^2 \tag{3.30}$$

C_{e50} represents the dose rate at half full effect and reflects the dose response on patient state. $U_{prop}(t)$ and $U_{remif}(t)$ are the effect site concentrations normalized with respect to the half of the effect site concentrations necessary to achieve the maximum effect. $C_{e,p}(t)$ and $C_{e,r}(t)$ are the effect-site concentrations of propofol and remifentanil, respectively, coming from the first order linear model. $C_{e50,p}$ and $C_{e50,r}$ are the propofol and remifentanil concentration required to reach half of the maximum effect over the BIS level. The coadministration of propofol and remifentanil does not influence the single drug pharmacokinetics, but there is a synergetic pharmacodynamic effect that is represented by β. $U_{50}(\phi)$ expresses the power of both drugs at the ϕ ratio as the number of units associated with the 50% of the maximum effect.

3.2. Patient dataset

The patient dataset used in this dissertation is the one used in [5] and is characterized in Table 3.1.

Table 3.1: Characteristic variables for the demographics and Hill function parameters of the considered set of patient (H: height, W: weight, G: gender).

Id	Age	H [cm]	W [kg]	G	$C_{e50,p}$	$C_{e50,r}$	E_0	E_{max}	β	γ
1	40	163	54	F	6.33	12.5	98.8	94.10	2.00	2.24
2	36	163	50	F	6.76	12.7	98.6	86.00	1.50	4.29
3	28	164	52	F	8.44	7.1	91.2	80.70	1.00	4.10
4	50	163	83	F	6.44	11.1	95.9	102.00	1.30	2.18
5	28	164	60	M	4.93	12.5	94.7	85.30	1.20	2.46
6	43	163	59	F	12.00	12.7	90.2	147.00	1.30	2.42
7	37	187	75	M	8.02	10.5	92.00	104.00	0.80	2.10
8	38	174	80	F	6.56	9.9	95.5	76.40	1.00	4.12
9	41	170	70	F	6.15	11.6	89.2	63.80	1.70	6.89
10	37	167	58	F	13.70	16.7	83.1	151.00	1.90	1.65
11	42	179	78	M	4.82	14.0	91.8	77.90	1.20	1.85
12	34	172	58	F	4.95	8.8	96.2	90.80	0.90	1.84

3.3. Control system

One of the most widely used control systems is the PID controller, which was explained in section 2.2.1, and the one chosen for this work because it is well-studied and easy to use.

The simulation schematic is represented in Figure 3.2, and it was designed with Simulink. The goal was to maintain the BIS value near the desired reference value during most part of the simulation. A BIS value between 40 and 60 suggests an appropriate level of general anesthesia [7], [52], [53]. Therefore, the chosen reference value for the BIS was 50.

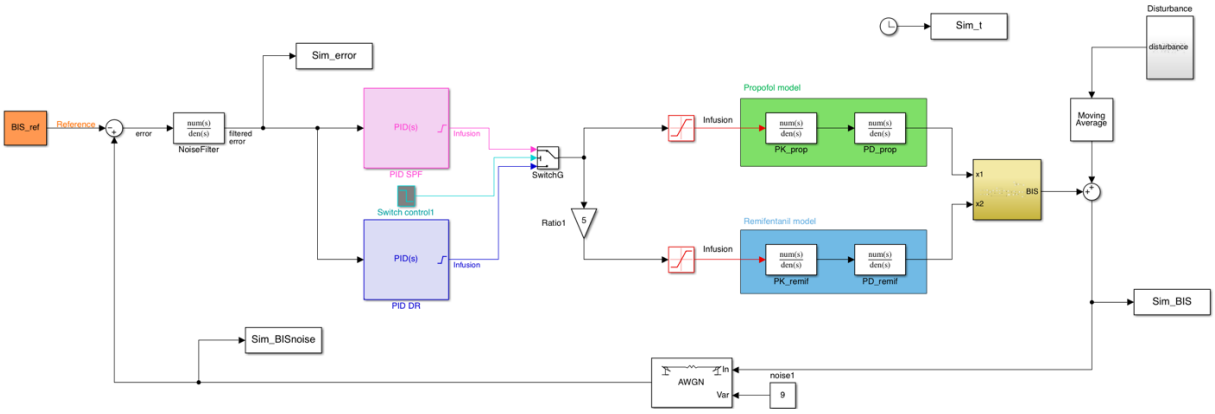

Figure 3.2: : Simulation schematic designed in Simulink for the automatic regulation of coadministration of propofol and remifentanil during anesthesia.

The feedback controller is a PID controller in ideal form with a filtered derivative term:

$$\mathrm{PID(s)} = \mathrm{P}\left(1 + \mathrm{I} \times \frac{1}{\mathrm{s}} + \mathrm{D}\frac{\mathrm{N}}{1 + \mathrm{N} \times \frac{1}{\mathrm{s}}}\right) \tag{3.31}$$

where P is the proportional gain, I is the inverse of $\mathrm{T_i}$ (the integral time) as per $\mathrm{I} = 1/\mathrm{T_i}$ and D is the derivative time. To avoid instability, a derivative filter was added, with the filter coefficient (N) fixed to 100, leading the derivative term to approximate zero at high frequencies.

A proportional-integral-derivative controller measures an output of a process and regulates its input with the goal of maintaining the output at a predefined point known as the set-point. The difference between the measured value and the set-point is the error. The error is handled in three distinct ways:

- P is a proportional controller and it responds to the absolute value of the BIS error at any point in time;
- I corresponds to the integration of the error in a given period of time, and it acts when there are values constantly below or above the desirable values;
- D takes into account the PID differential, and it will act more quickly to variations (differentials) that are detected.

In order to achieve better performance, two different PID controllers for two separate tasks were necessary. One for the set-point following (SPF) and the other for disturbance rejection (DR). The SPF task matches the induction phase of anesthesia and the DR task matches the maintenance phase, which means maintaining the BIS value as close as possible to 50 at all times.

A gain scheduling approach was used to integrate both control stages in the control system using the tracking (TR) mode of Simulink. So during the induction phase, the SPF PID block performs the control action while the DR PID block is in TR mode. The TR mode allows the controller to adjust its internal state by changing its integrator output so that the block output tracks the output of the SPF PID

block. When the induction phase terminates, the DR PID block changes from tracking mode to control mode.

The SPF task was defined as having a duration of 10 minutes, and the DR task and the optimization phase had a duration of 90 minutes. Also, a simple disturbance profile of amplitude 10 acting directly on the process variable was used for the DR task and the optimization phase, followed by another step of amplitude -10 after 20 minutes.

Regarding the remaining blocks – PK, PD and Hill – they correspond to the three components of the patient model; Noise was used to simulate the presence of measurement noise in the real BIS signal. The Noise added consisted of an additive white Gaussian block with zero mean value and a standard deviation that can be chosen by the user (a standard deviation of 3 was employed as the default). Subsequently, a block (*3.32*) that acted as a filter was added to diminish the effects of measurement noise on the controller's performance.

$$F = \frac{1}{(T_f \times s)^2} \tag{3.32}$$

The saturation blocks, represented in red in the schematic of Figure 3.2, limit the values of the infusion rates between 0 and 6.67 mg/s for propofol and between 0 μg/s and 16.67 μg/s for remifentanil. These upper limits were established by taking into account the maximum infusion rate of a standard clinical pump, which is 1200 mg/hr, as well as the concentrations of propofol (20 mg/ml) and remifentanil (50 μg/ml).

Indeed, a propofol-remifentanil infusion ratio was adopted to allow the anesthesiologist to choose the appropriate opioid-hypnotic balance. The ratio was calculated by dividing the remifentanil infusion rate in μg/s by the propofol infusion rate in mg/s. The ratio value in the suggested control system can be chosen between 0.5 and 15 according to [5]. The choice depends if the anesthesiologist prefers a hypnotic component more predominant in cases of little painful stimulation or of concomitant use of loco-regional analgesics; or if anesthesiologist prefers an analgesic component more predominant in cases of surgical phases that involve strong painful stimulation. For this work, a ratio of 0.5 was used.

3.4. PID controller parameters

The methodology followed for tuning the PID controller consisted of using a genetic algorithm (GA) to minimize the integrated absolute error (IAE) of the step response of the system. GAs are frequently used to generate high-quality solutions to optimize and search problems. It is worth highlighting that GAs do not require a starting point; all that is required is to define the search space, which is easily given by considering the physical meaning of the parameters.

In anesthesia, a satisfactory clinical outcome is defined as a fast transient response that does not involve a large overshoot in the induction phase and a BIS that is kept as close to the target value as possible in the maintenance phase, resulting in a low IAE value. IAE is given by equation (3.33)

$$IAE = \int |e(t)|\, dt \tag{3.33}$$

3.5. Performance of the controller system

Several indexes can be used to assess the control system's performance. These include the median performance error (MDPE), the median absolute performance error (MDAPE) and wobble.

The MDPE is a measure of bias and describes whether the measured values are systematically above or below the target value, which is 50. MDPE of the i^{th} subject is given by equation (3.*34*):

$$\mathrm{MDPE_i} = \mathrm{Median}\{\mathrm{PE_{ij}}, \mathrm{j} = 1, \dots, \mathrm{N_i}\}, \tag{3.34}$$

where $\mathrm{N_i}$ is the number of PE values obtained for the i^{th} subject. PE is the performance error and it is calculated using all the observations in the simulation period.

$$\mathrm{PE} = \frac{(\text{measured value} - \text{target value})}{\text{target value}} \times 100 \tag{3.35}$$

The MDAPE reflects the inaccuracy of the control method for each subject. MDAPE of the i^{th} subject is given by equation (3.*36*):

$$\mathrm{MDAPE_i} = \mathrm{Median}\{|\mathrm{PE_{ij}}|, \mathrm{j} = 1, \dots, \mathrm{N_i}\} \tag{3.36}$$

Wobble is related to the oscillation of the controller behavior. The percentage wobble is calculated for the i^{th} subject as shown in equation (3.*37*):

$$\mathrm{wobble_i} = \mathrm{Median}\{|\mathrm{PE_{ij}} - \mathrm{MDPE_i}|, \mathrm{j} = 1, \dots, \mathrm{N_i}\} \tag{3.37}$$

Aside from this, the Settling Time during the induction phase was estimated. The response is considered to have settled when the error |BIS(t) – 50| becomes smaller than 0.02 (2%) of its peak value. The percentages of time during which the BIS value is above 70 or below 40 are also indicated. When BIS exceeds 70, there is a larger chance of consciousness and the capacity for recall. Bispectral index less than 40 concurrent with hypotension is associated with 90-day postoperative mortality [54], and indicates a deep hypnotic state, loss of memory function and an increase of burst suppression.

3.6. Disturbance profile

To test the robustness of the controller, a more realistic, hence more complex, disturbance profile was supposed to be used in the performance evaluation simulations. It was based on the one used in [8], which a BIS offset time profile was created to mimic a general surgical stimulation profile . Each segment represents a typical step in the majority of surgical procedures, including intubation (A), surgical incision (B), abrupt stimulus (C), short-lasting large stimuli (D,E,F), and closing (G), as shown in Figure 3.3.

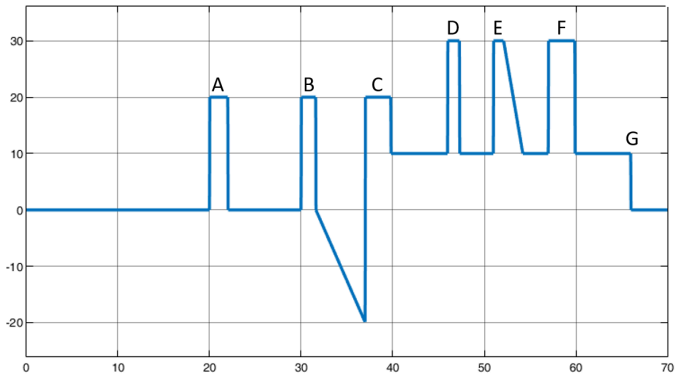

Figure 3.3: Default disturbance profile used in this work for the performance evaluation. The scheduling of each disturbance was: A-20min, B-30min, C-37min, D-46min, E-51min, F-57min, G-66min.

The offset BIS values of the profile above were adjusted to the half of the value, as shown in Figure 3.4. In Figure 3.3, for the BIS offset to be 20 means that the measured value was 70 and the set-point 50 (70-50=20). This change is only a simulation if the measured value was 60 instead of 70 in the initial step represented as A, and so on. The scheduling of each disturbance was: intubation - 1200s, surgical incision – 1800s, abrupt stimulus – 2220 s, short-lasting large stimuli – 2750s, 3060s and 3420s, and closing – 3960s.

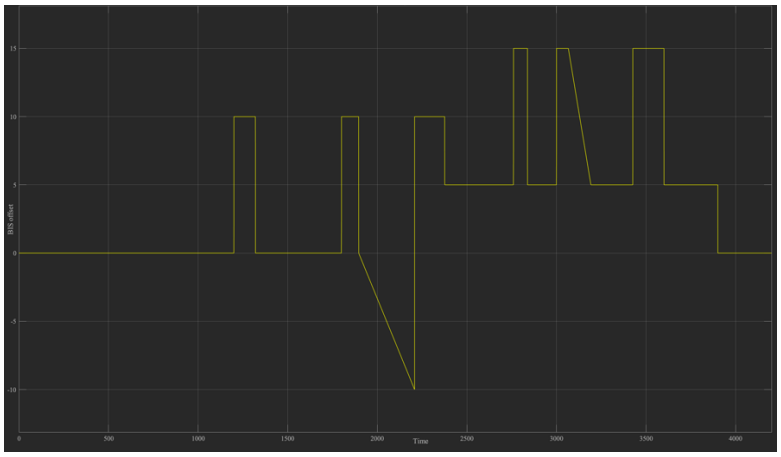
Figure 3.4: Same disturbance profile as the one Figure 3.3 but with BIS offset values adjusted to half. X-axis in seconds.

4. Results, Data Analysis and Discussion

The tuning of the PID controller is the main part of controlling any plant process through it. Here, this tuning was performed based on a genetic algorithm. The maximum time for the genetic algorithm was 1000 seconds (approximately 16.7 minutes) for each part, which in total was 70 minutes. Each part consists in the set-point following task for females, the set-point following task for males, the disturbance rejection task for females and the disturbance rejection task for males. The SPF task matches the induction phase of anesthesia and the DR task matches the maintenance phase.

The optimal PID parameters, as well as the filter time constant (T_f) are shown in Table 4.1 for both SPF and DR tasks. The GA was implemented in the Matlab Global Optimization Toolbox, without including measurement noise.

Table 4.1: PID optimal parameters and filter time constant obtained with the tuning algorithm described. Values presented for male and female case of both controllers (SPF PID and DR PID). (M: male, F: female, P: proportional, I: integral, D: derivative, Tf: filter time).

	SPF		**DR**	
	M	**F**	**M**	**F**
P	0.9000	0.8328	0.6557	0.1202
I	0.1178	0.2440	0.5343	0.8209
D	7.8319	9.3319	0.3207	18.6336
T_f	0.9243	0.8558	0.9243	0.8558

Figures below (Figure 4.*1* and Figure 4.*2*) show the plot of the BIS (with and without added noise) for males and females, over the simulation time, respectively. To minimize the amount of time lost before the surgery can begin, it is ideal to induce the patient into an operational DoA as soon as possible. As a result, it is desirable that the patient achieves the BIS=50 target and maintains this value without experiencing significant undershoots and overshoots. Indeed, the BIS value begins to decrease in the induction phase, taking a short time for the target value to be reached without appearing to have excessive undershoots. In both PID Figures, Figure 4.*1* and Figure 4.*2*, the BIS in the is below 40 first seconds but quickly manages to stabilize near the desired value. In the case of men (Figure 4.1) there is a later relapse of BIS, at 600 seconds which is at the transition time from SPF to DR. In women, a BIS below 30 in the induction phase should be avoided.

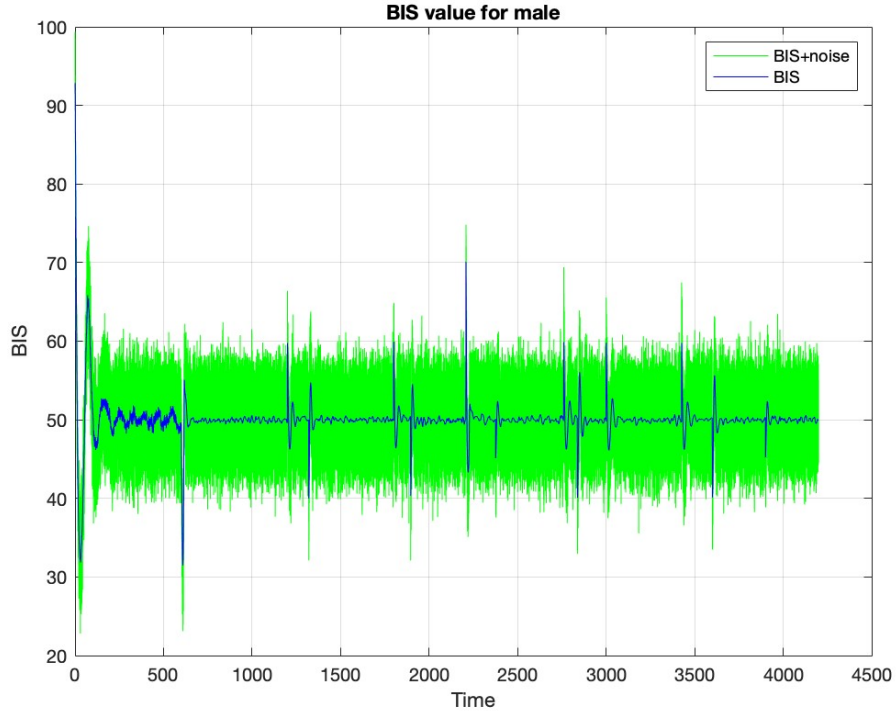

Figure 4.1: BIS over time with and without noise for males (Id=5, 7, 11). Time is seconds.

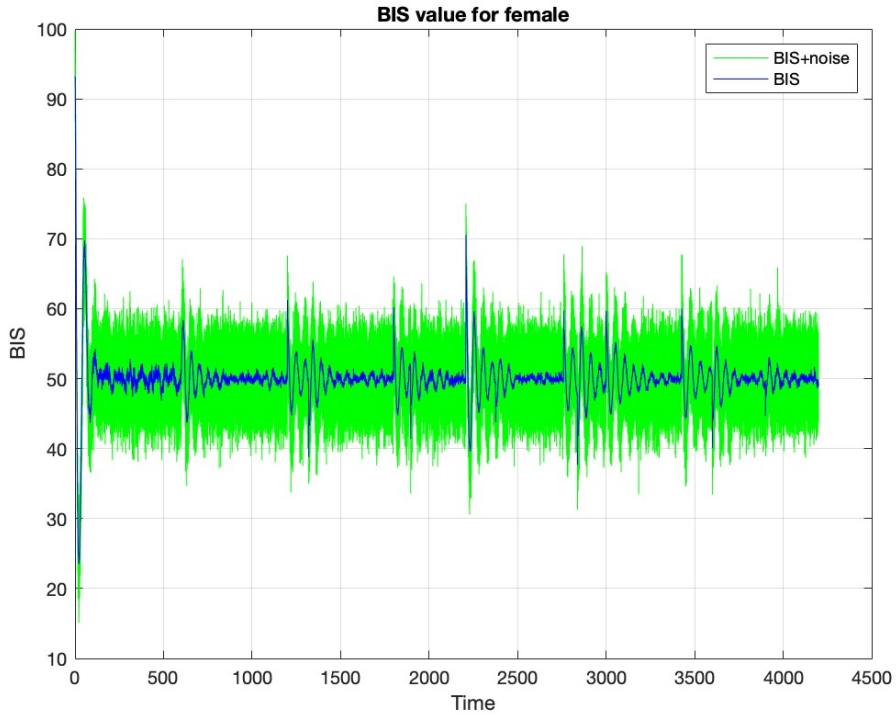

Figure 4.2: BIS over time with and without noise for females (Id=1, 2, 3, 4, 6, 8, 9, 10, 12). Time is in seconds.

During the maintenance phase, the disturbance (yellow line in Figure 4.3) is introduced which explains the “ups and downs” that are part of the procedure. The BIS (blue line in Figure 4.3) is approximately 50, with no major oscillations.

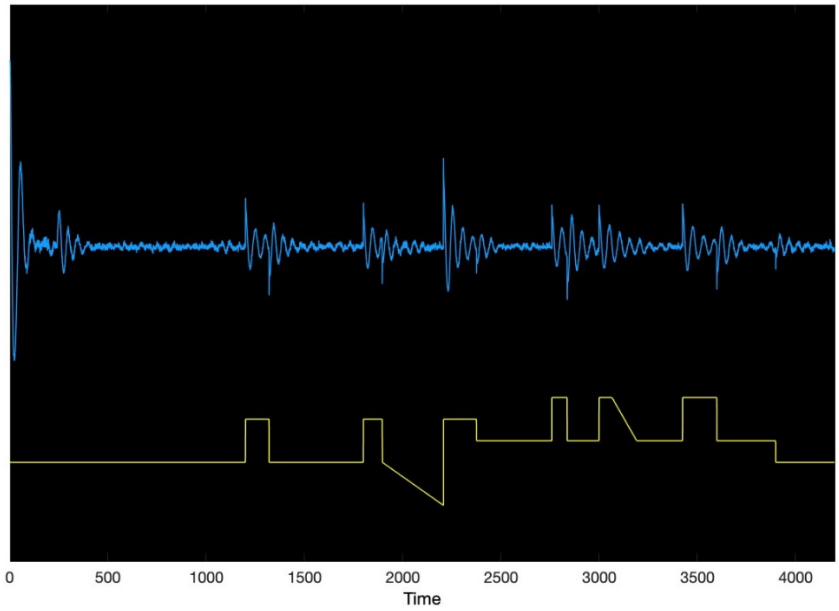

Figure 4.3: Blue line represents the BIS for females and yellow line represents the disturbance profile. Time is in seconds.

Propofol takes effect quickly. Indeed, in men (Figure 4.4) it reaches 3 μg/ml in the very first seconds. The concentration in the induction phase takes a while to take effect and the signal is a little noisy. But when disturbance is introduced (at 600 seconds), in the maintenance phase, there is an increase of the concentration of propofol. At the time of the surgical incision (1800s), the concentration tends not to vary much until the patient is "closed". A small change can be seen at 2220 s due to the abrupt stimulus.

In case of women (Figure 4.6), it takes a while to reach 3 μg/ml of propofol in the induction phase, which is the maximum. At the end of intubation, the concentration also tends not to vary much but it is lower in women than in men and the signal is very noisy. Also, due to an abrupt stimulus, a small change can be seen at 2220 s.

The recommended concentration of propofol to maintain adequate depth of anesthesia when combined with an opioid varies from 2.5 to 8 μg/ml [55], which is confirmed in Figure 4.4 and Figure 4.6. The mean Ce (effect site concentration) for recovery of consciousness is <1.2 μg/ml (varies with high opioid use). The values of Figure 4.4 and Figure 4.6 never reach a value near 1.2 μg/ml.

The remifentanil concentration (ng/ml) is initially high for both men and women, being higher in women (Figure 4.7). Throughout the induction phase (until the 600s), concentrations are higher in women. In men (Figure 4.5) there is a significant increase in remifentanil concentration when a disturbance is introduced, while in women this concentration is more "stable". In both cases several peaks can be seen in the graphic of the remifentanil concentration, which happen at each surgical step - intubation (1200s), surgical incision (1800s), abrupt stimulus (2220s), short-lasting large stimuli (2750s, 3060s and 3420s). In these phases, the concentration of remifentanil increases dramatically (and then decreases) in men (Figure 4.5).

In [56], the effect site concentration for remifentanil for orotracheal intubation with a target propofol effect-site concentration of 5.0 μg/ml were 6.85 ng/ml. In fact, the remifentanil concentration values seem to be similar to what is indicated. However, there is no study that indicates a direct relationship, i.e. ratio, between the amount of propofol and the amount of remifentanil. Consequently, in this study, it is not possible to make such a comparison because the ratio can be adjusted according to the desired effect and the type of surgery. As mentioned before, the ratio allows the anesthesiologist to choose the appropriate opioid-hypnotic balance.

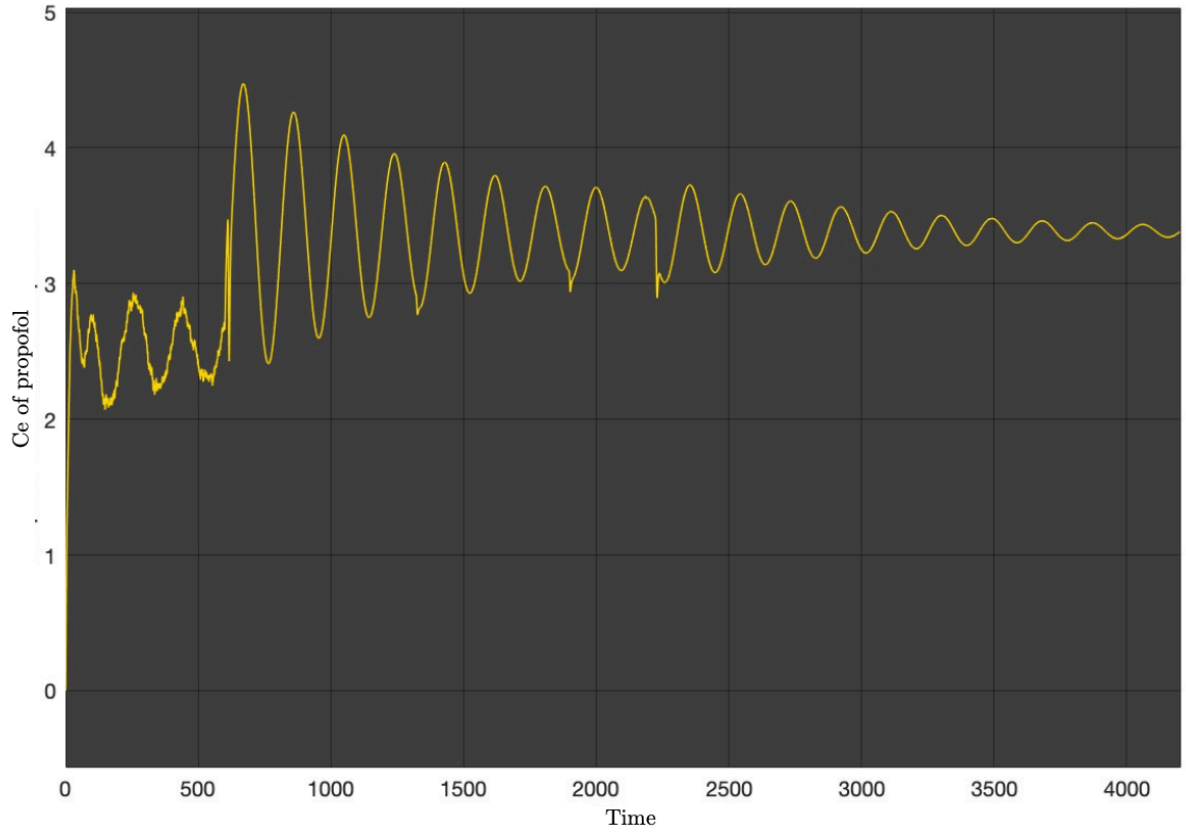

Figure 4.4: Effect site concentration of propofol (μg/ml) for males over time (s).

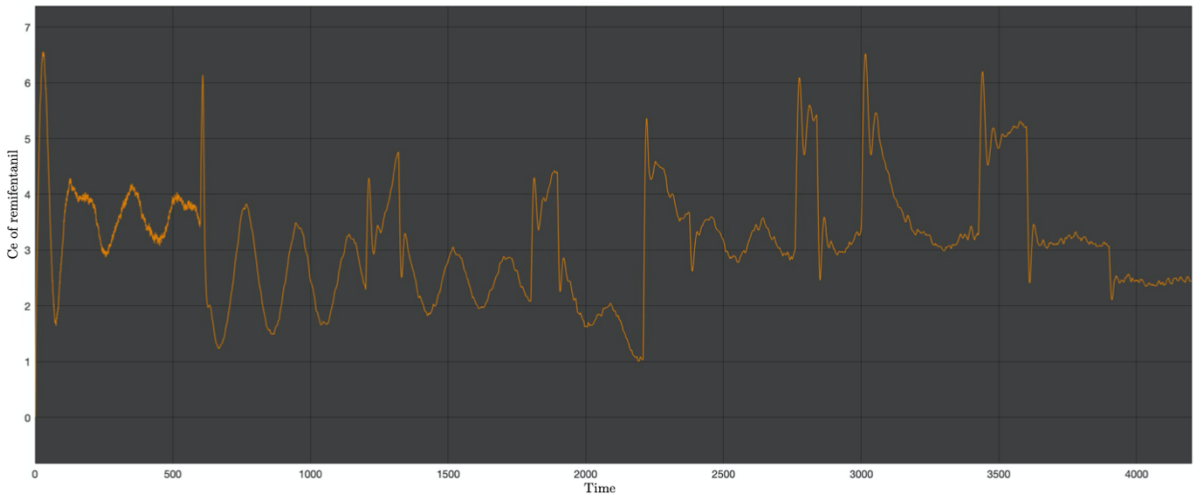

Figure 4.5: Effect site concentration of remifentanil (ng/ml) for males over time (s).

In women, the propofol concentration tends to stabilize in the maintenance phase and is lower compared to the induction phase.

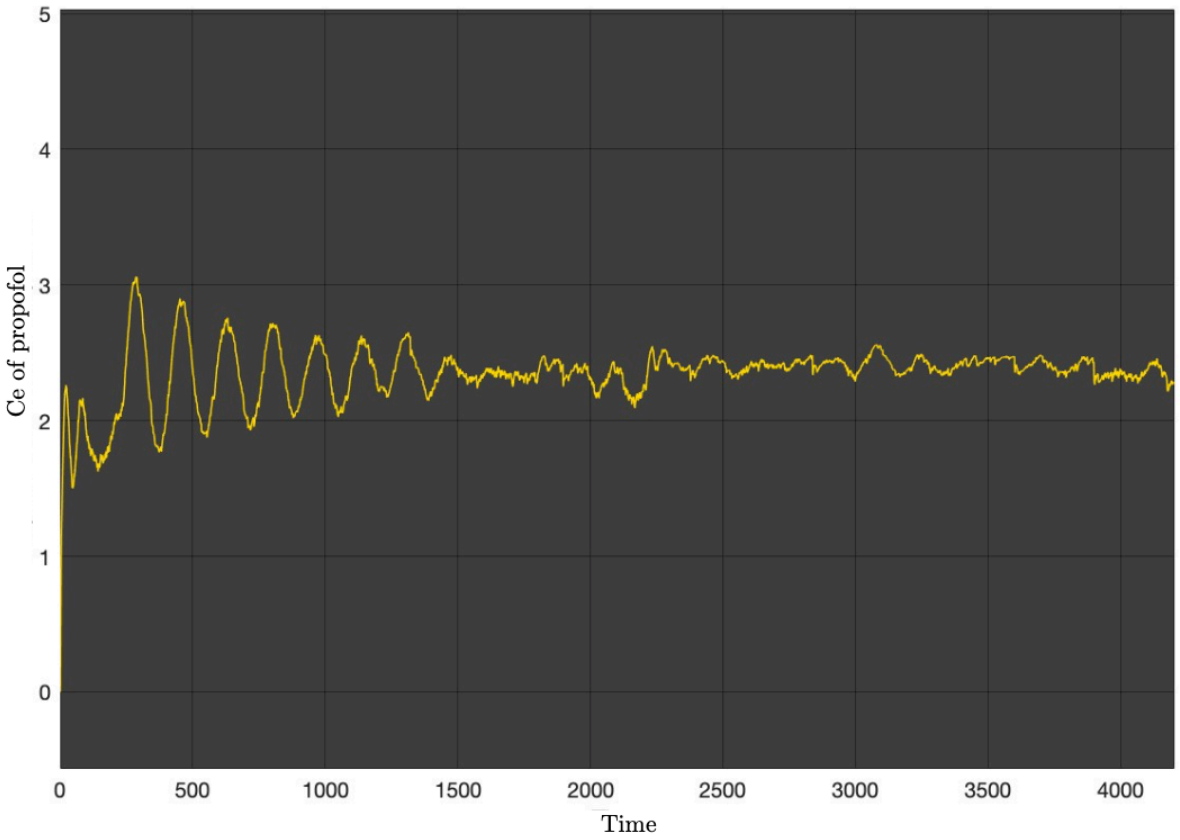

Figure 4.6: Effect site concentration of propofol (μg/ml) for females over time (s).

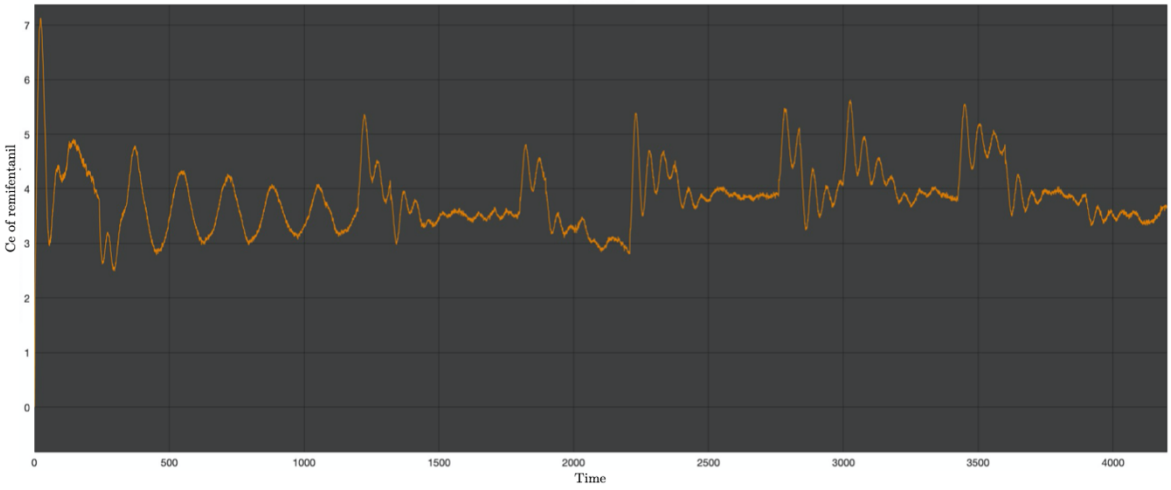

Figure 4.7: Effect site concentration of remifentanil (ng/ml) for females over time (s).

The performance indexes obtained were averaged over male and female patients and are presented in Table 4.2.

Table 4.2: Average of the performance indexes over the results obtained for the whole set of male patients (Id=5,7,11) and female patients (Id=1-4,6,8-10,12). (IAE: integrated absolute error, ST: settling time, MDPE: median performance error, MDAPE: median absolute performance error, BIS=bispectral). IAE is not time normalized.

	SPF		**DR**		**Total**	
	M	**F**	**M**	**F**	**M**	**F**
IAE	68644.9	69974.8	154549.1	279242.0	223194	349216.8
ST (min)	3.75	3.83	NA	NA	NA	NA
MDPE (%)	0.12	0.55	-0.08	-0.10	-0.08	-0.08
MDAPE (%)	4.88	3.49	0.40	1.31	0.43	1.38
Wobble (%)	4.84	3.55	0.39	1.31	0.42	1.37
BIS>70 (%)	2.64	4.15	0.004	0.005	0.15	0.24
BIS<40 (%)	11.4	10.29	0.26	0.06	0.90	0.64

In Table 4.2, the worst-case results obtained with the set of the 12 individual patients are presented. It is evident that the controller performs better during the maintenance period compared to the induction phase.

The magnitudes of all indexes should be as small as possible. In terms of MDAPE, a system with a lower MDAPE should have better control over the desired BIS value. Indeed, this corresponds to reduced periods of excessive anesthesia (BIS<40) or reduced risk of awareness (BIS>70) [8]. The system has better control over the desired BIS value in the maintenance phase (DR) even though the disturbance was introduced. This is confirmed by the MDAPE with a lower probability of overshoot and undershoots in the DR task. The high probabilities of a BIS<40 and a BIS>70 in the SPF task are due to an error that is larger initially.

The system is quick to stabilize, taking less than 4 minutes: 3.75 minutes (225s) for males and 3.83 minutes (229.80s) for females, which can also be confirmed by Figure 4.1 and Figure 4.2.

When using the genetic algorithm, it is necessary to choose the appropriate values of the boundaries. In this simulation the following were used lb=[0 0 0 0] and ub=[1 1e1 1e2 1]. lb means lower boundary and ub means upper boundary. Each value represents the boundary for P, I, D and T_f, respectively. These used boundaries were defined by an empirical trial an error methodology.

The system can also be adjusted for a single patient as observed in Figure 4.8, which shows the plot of the BIS for patient 5 who is a male. The graph corresponds to what is expected, since BIS can mostly be kept between 40 and 60 during the maintenance phase. During the induction phase the system is quick to stabilize at 50, which was the chosen target value. The integral term looks similar SPF but other than that, the values vary. By making the adjustment for each patient, the drug infusion rates are more precise. However, we can see in Figure *4.8* for patient 5 that he achieves a BIS<30, which never happened with the PID values calculated for the average male. Probably if the genetic algorithm ran for a longer period of time, these cases could be avoided.

Table 4.3: PID optimal parameters and filter time constant obtained with the described tuning algorithm. Values presented for all male patients (average) and one male patient (Id=5).

	SPF		**DR**	
	M	**M (Id=5)**	**M**	**M (Id=5)**
P	0.9000	0.9595	0.6557	0.3576
I	0.1178	0.1190	0.5343	1.9493
D	7.8319	9.4725	0.3207	3.7511
T_f	0.9243	0.9586	0.9243	0.9586

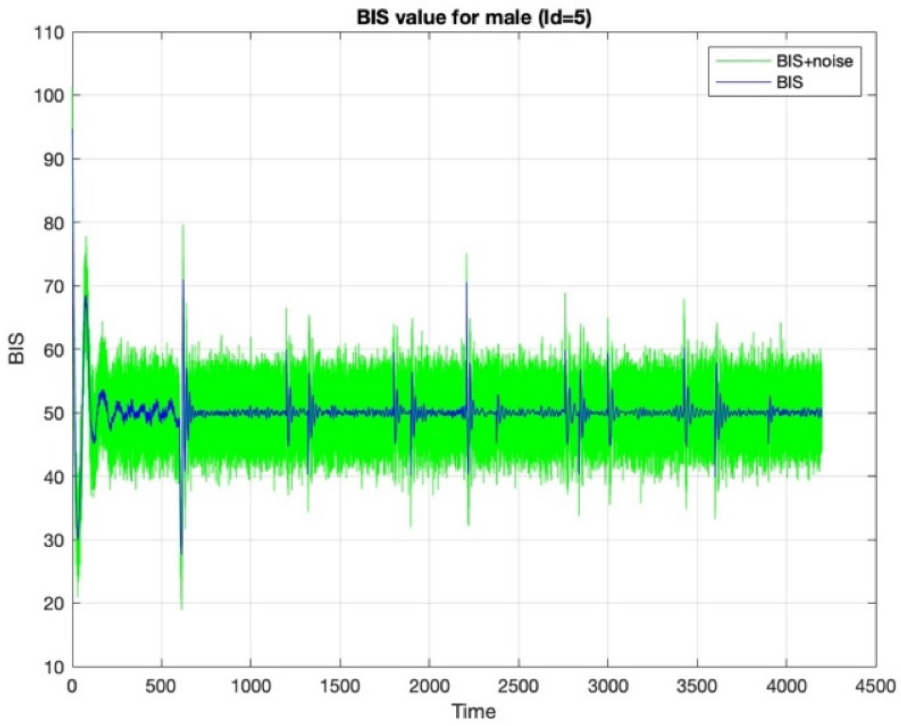

Figure 4.8: BIS over time, with and without noise, for one patient (Id=5, G=male). Time is given in seconds.

Since there is no other study for propofol and remifentanil that use the same metrics, it is not possible to make a direct comparison between our model and others in the literature.

5. Conclusion

With this work, a new PID-based control scheme to regulate the depth of hypnosis in anesthesia using propofol-remifentanil coadministration has been designed. The tuning of the PID parameters has been performed by using genetic algorithms for both the infusion and the maintenance phases in order to minimize the worst-case integrated absolute error in a set of patients that is representative of a wide population.

The suggested control allows the anesthesiologist to choose the appropriate drug infusion ratio during surgery to manage the opioid-hypnotic balance. Nevertheless, both excessively large and excessively small values of BIS need to be avoided. To prevent dangerous hypotension, a BIS level equal to or below 40 should not be reached. The probability of the BIS being less than 40 is relatively high during the induction phase (11.4% for males and 10.29% for females) compared to the maintenance phase (0.26% for males and 0.06% for females). So it is important to improve the system with this in mind. It is essential to guarantee both a fast set-point tracking with a small undershoot in the induction phase and in rejecting disturbances as fast as possible in the maintenance phase.

The induction phase was set to 10 minutes, but the settling time was less than 4 minutes, indicating how fast the system was in finding the BIS 50. During the maintenance phase, a constant BIS level, equal to 50, should be maintained, which was achieved.

The behavior of the controller did not present significant overshoots while recovering from the disturbances but had some undershoots specially in the induction phase, as it was said before. With some future developments, this can be avoided by further exploring the functionalities of the GA and other optimization algorithms.

The maximum time for the genetic algorithm was 1000 seconds (approximately 16.7 minutes), which is a long process when multiple attempts have to be made. The simulation took more than 1 hour (1000 seconds for each part – SPF for women, SPF for men, DR for women and DR for men). However, it is known that the longer the time, the better the values obtained by the algorithm.

This work does contribute to future research in the field of closed-loop control in anesthesia, particularly by empowering future research with important tools such as a comprehensive simulation scheme to which adaptations can be made (especially within the PID parameters), which includes a customized PID controller – gender-specific or patient-specific – separately tailored for both phases of anesthesia.

Future work could include the physiological variables such as heart rate, blood pressure, oxygen saturation in the blood, and carbon dioxide concentrations in the blood or end-tidal. For instance, data from a BP and an EMG sensor could be included. Also, analgesia monitoring could be added, for example, the Richmond Agitation and Sedation Scale (RASS).

Additionally, the system could potentially be applied to other drugs as control variables such as atracurium, to control the other component of anesthesia, such as the neuromuscular blockage. Also, it could be tested with children's data and the system could be adapted if necessary.

To conclude, a bolus could be implemented in Simulink, so that the anesthesiologist could administer more drugs in cases where the BIS is above 70. Alternatively the system could calculate the required quantity of drugs and administer them automatically according to BIS while taking into account the physiological variables (which would be more complex but accurate).

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