A Comprehensive Review on Automated Control of Anesthesia: Recent Methods, Challenges and Future Trends

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Abstract

The safe and personalized administration of anesthetic drugs is a significant concern in clinical practice, and automated control of anesthesia can address this issue by reducing human error, such as under- or over-dosing. This has the added benefit of allowing anesthesiologists to focus on more critical tasks and emergency management. The advantages of automated anesthesia delivery are not limited to anesthesiologists alone, as patients also benefit from the personalized and safe administration of drugs. This article offers a concise overview of the latest developments in closed-loop anesthesia delivery control systems. These systems include a range of elements such as monitoring depth of anesthesia, patient modeling, control techniques, safety systems, and clinical trial validation. Although anesthesia control has undergone significant changes over the years, a fully integrated system remains elusive. To move towards personalized patient care, it is important to assess the current technological limitations, societal considerations, and implementation hurdles, in order to identify new challenges that need to be addressed by intelligent systems. The convergence of clinical and engineering approaches facilitated by automation provides a foundation for research in the field of clinical anesthesia control. This union is crucial to guaranteeing patient safety, cost-effectiveness, and efficient performance by clinicians.

Keywords

Closed-loop control, Drug delivery control, automated anesthesia delivery.

I. Introduction

The well-being and healthcare of patients are fundamental aspects of our society. In the field of surgery, where millions of people undergo operations worldwide on a daily basis, effective control of total intravenous anesthesia is crucial. Inadequate intra-operative anesthesia or postoperative pain treatment can lead to post-operative complications. Therefore, decision support systems have a crucial role in maintaining a positive balance between benefits and risks, with the collaboration of both medical and engineering disciplines [1]. Studies suggest that automated control of drug dosing systems for anesthesia results in significantly better performance than manual control administration. Decision actions must

address several issues, such as increased clinical workload, varying anesthesia infusion practices, which may depend on the doctor's expertise, and the frequent use of a constant drug infusion rate leading to slight overdosing. The main factors motivating the automation of anesthesia administration are a standardized, high-quality anesthesia decision support system, reduction of post-operative effects, individualized and adapted drug infusion, and robust maintenance of target values [2].

The purpose of this review is to provide a comprehensive overview of the ongoing research in the field to readers who are not familiar with it. By introducing Important information from different facets of the field, we aim to create a foundation and update on the current state of the field. Section III will briefly introduce the monitoring, modeling, and control methods that are commonly used in physiological systems. The detailed mathematical models, Which have been thoroughly documented in the references cited, will be presented in a concise manner. Sections IV will highlight the challenges encountered in automated anesthesia. In Sections V-VI, we will examine several critical aspects of the research that have broader implications in physiological control and suggest possible directions for future studies.

II. Preliminaries

Anesthesia refers to the absence of sensation and can be defined as an unresponsiveness to and lack of memory of painful stimuli. In 1842, inhaled ether was used by Crawford Williamson Lang to perform the first application of anesthesia [3]. The administration of anesthetic drugs in medical settings induces a general or local anesthetic effect on the patient's body to achieve anesthesia. This results in unconsciousness and may also lead to a complete lack of bodily movement, this is known as "general anesthesia". Two types of anesthetic drugs may be given to patients during general anesthesia: (i) inhaled anesthetics, The two types of anesthetics are (i) inhalational anesthetics, which are administered in the form of gases or vapors, and (ii) intravenous anesthetics, which are administered via injection. Anesthesia induction often involves the use of intravenous drugs because they provide a smoother and more rapid induction than most inhaled agents. Intravenous anesthetics may also serve as a maintenance method for anesthesia, whether used alone or in combination with inhaled agents. [4].

Intravenous Anesthetic drugs can be classified based on their physiological effects into: (i) hypnotic drugs, (ii) analgesic drugs, and (iii) neuromuscular blocking (NMB) drugs. Hypnotic drugs are used to induce unconsciousness during surgery by numbing the brain. Propofol is presently the most frequently utilized intravenous hypnotic drug because of its swift metabolism and distribution within the body. Compared to other hypnotic drugs, it poses a lower risk of adverse side effects, thanks to its reduced tissue accumulation [4]. The second category, analgesics, mitigate the sensation of pain. The most commonly employed type of analgesics are opioid analgesics, like remifentanil. NMB drugs, the third type of anesthetics, induce paralysis in the affected skeletal muscles by Preventing the transmission of nerve signals at the point where nerves meet muscles, known as the neuromuscular junction. NMB drugs are effective in aiding endotracheal intubation and mechanical ventilation [3]. Figure 1 demonstrates how the three categories of drugs employed in anesthesia aid in achieving the three primary objectives of general anesthesia: (i) hypnosis, or unconsciousness induced by hypnotic drugs, (ii) analgesia, or pain insensitivity induced by analgesic drugs, and (iii) muscle relaxation induced by NMB drugs.

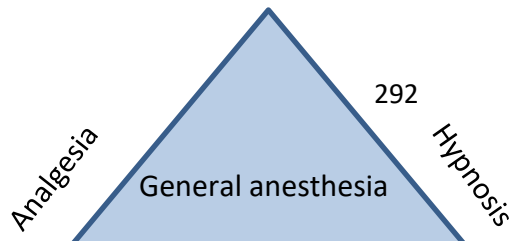

Fig.1 Three key components of clinical anesthesia

Administering general anesthesia involves three primary stages: induction, maintenance, and emergence. The induction stage is considered the most critical, as it involves administering sufficient doses of hypnotic, analgesic, and NMB drugs to produce the three fundamental components of anesthesia, which allow for the placement of an endotracheal tube to facilitate mechanical ventilation by the anesthesiologist. After induction, the maintenance phase begins, during which the anesthesiologist maintains a balance in the use of anesthetic agents, intravenous fluids, and other drugs to maintain hemodynamic stability, organ function, and an adequate level of hypnosis [5]. The final phase is the emergence phase, This phase occurs towards the end of the surgery, during which the patient is gradually brought out of anesthesia to regain normalcy. During the emergence phase, the neuromuscular blockade is fully reversed, spontaneous ventilation and reflexes return, and the patient's hemodynamic stability and physiological functions are maintained to ensure a safe and comfortable recovery [5].

A. Administrating control of anesthesia

At present, anesthesia is delivered through manual means, either by an anesthesiologist or a physician in the ICU, who rely on continuous visual monitoring of the patient's brain activity on the EEG or indirect measures like monitoring muscle tone or heart rate. Advancements have been made in the field of brain-machine interface, wherein the patient's neural activity is automatically monitored, and the infusion rate of the anesthesia drug is modified based on real-time neural activity [6]. Although numerous attempts have been made to deliver anesthesia to patients in a closed-loop manner, as depicted in Figure 2, there is currently no established technique available for real-time clinical application, largely because legal regulations pose a significant hindrance. For closed-loop control of the anesthetic drug to be effective, the feedback report on the clinical effect must constantly adjust the anesthetic drug concentration to enhance drug administration and improve safety. Therefore, the safety of the patient during anesthesia administration is a major concern for clinicians [7].

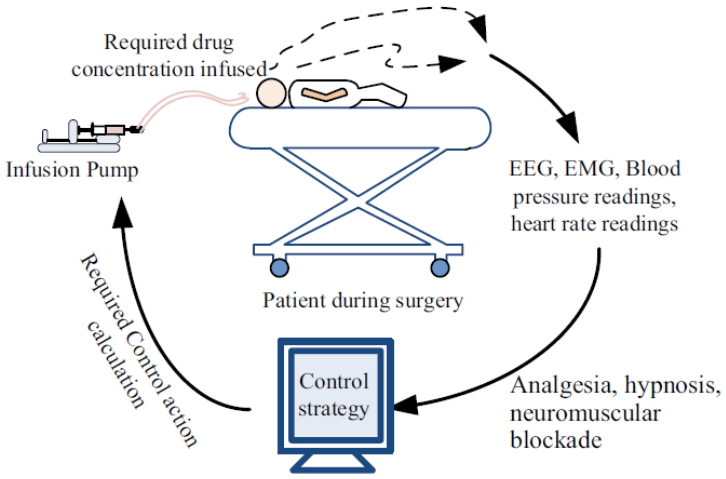

Fig. 2 The fundamental structure of the closed loop control system for administering anesthesia

B. Compartmental Models

The mechanism of action of a drug can be explained by dividing it into two components: pharmacokinetic (PK) and pharmacodynamic (PD). The PK model is typically linear and employs population models to characterize the drug concentration in the body. Biometric variables such as age, height, weight, and gender are connected to the projected drug concentration and clearance in various parts of the body through coefficients. Anesthesia PK models generally have three compartments, namely the blood-compartment, muscle, and fat, as well as a hypothetical compartment that transfers the concentration from the central compartment (blood) to the effect site (brain). Various equations can be derived from this model by extracting transfer functions [3]. Conversely, the PD model is highly nonlinear and accounts for the variability between and within patients [1] [8]. It follows a Hill curve (fig. 3), which is a sigmoid curve that links the effect-site concentration to the actual effect in the body. The curve demonstrates the patient's sensitivity to the drug, which can vary significantly. The Hill curve, in its generic form, displays the relationship between drug effect and drug concentration, with the slope representing the derivative of the effect with respect to concentration. This slope is also an indicator of the degree of steepness of the curve [9].

III. Automated anesthesia

Creating automated systems for administering anesthesia involves three main elements: measurement or monitoring, modeling, and control.

A. Monitoring

For a successful anesthesia experience during surgery, the anesthesiologist must estimate the suitable the quantity and timing of administering drugs. for each stage of the procedure. They depend on various physiological parameters and clinical signs. to make such estimations. Although clinical signs like pupil dilation, blood pressure, heart rate, tearing, and sweating can offer some helpful insights into the sufficiency of anesthesia [10]. Although physiological monitors, such as electroencephalography (EEG), electromyography (EMG), blood pressure, electrocardiography (ECG), and oxyhemoglobin saturation, provide a more comprehensive view, Additionally, Measured indicators like bispectral index (BIS), surgical stress index (SSI), auditory evoked potential (AEP), and entropy can offer more precise information regarding the patient's condition [11]. Analyzing EEG is a prevalent technique for precisely evaluating anesthesia administration, as EEG signals reflect the electrical activity occurring in the cerebral cortex, moreover the waveform features differ based on the type and amount of the anesthetic drug administered [12]. Devices used for signal monitoring, such as the (BIS) monitor, Narcotrend monitor, Cerebral State Monitor (CSM), and AEP monitor, are employed to gauge and quantify the EEG signal, offering an alternative means of measuring the adequacy of anesthesia. The Bispectral Index (BIS) is a critical measure that is strongly associated with the level of consciousness. BIS measurements are deemed valuable information for anesthesiologists during anesthesia, and clinical studies have indicated that it has the potential to enhance patient safety. The BIS index scale ranges from 0 to 100, where 100 indicates full consciousness, and 0 represents an isoelectric EEG. The BIS index decreases with an increasing concentration of anesthetic drugs [13]. The patient's state for different BIS index ranges and their effects on surgical memory are shown in Fig. 4. Typically, BIS values between 40 and 60 are deemed adequate for general anesthesia.

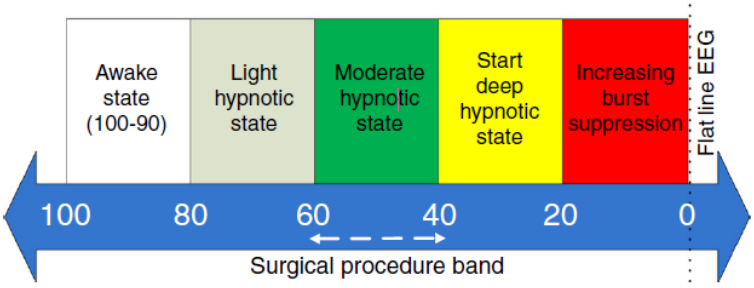

FIG 3. BIS index range and patient's state

The raw EEG data can be significantly influenced by various factors, which may include patient's (age, race, gender, low core body temperature), imbalances in acid-base levels, low blood sugar levels, certain drug administration (such as neuromuscular blocking agents), and brain ischemia, among others. In addition, the effectiveness of manual infusion systems and the ability to maintain optimal closed-loop management of anesthesia may be limited by the calibration range of DoA monitors and the variability in patients' response to medication. All of these factors and their interactions may pose challenges to achieving optimal anesthesia outcomes [14].

The interest in using PSI algorithm-powered equipment designed to monitor patient condition has grown because they are more susceptible to fluctuations in sedation/hypnosis status and consistently respond well to different anesthetic agents, making them a preferred alternative to BIS monitors [15]. Readers who wish to obtain more comprehensive information on anesthesia monitoring are advised to refer to the vast literature available on the subject (e.g [16]).

B. Modeling

In order to accurately administer drugs based on BIS and other measures, we need a comprehensive mathematical model that encompasses all elements of anesthesia is required. This model must account for relevant physiological parameters and the diverse dynamics associated with sedation, pain control, and muscular immobility states. In the following sections, we will provide a brief overview of the well-known anesthesia models.

1) Pharmacokinetic model

A pharmacokinetic model for a drug is a mathematical equation that establishes a relationship between the drug's concentration Cp(t) (mg/ml) in the blood plasma and the infusion rate I(t) (mg/min) of the drug into the central compartment [17]. By creating equations that maintain equilibrium for the amount of drug (xi in mg) present in each compartment, compartmental models for pharmacokinetics are constructed. Hence, the PK model in Figure 4 is governed by equations that can be expressed as follows:

$$\dot{x}_1 = \frac{I(t)}{V_1} - k_{12}x_1 - k_{13}x_1 - k_{10}x_1 + k_{21}x_2 + k_{31}x_3 \quad (1)$$

$$\dot{x}_2 = k_{12}x_1 - k_{21}x_2 \quad (2)$$

$$\dot{x}_3 = k_{13}x_1 - k_{31}x_3 \quad (3)$$

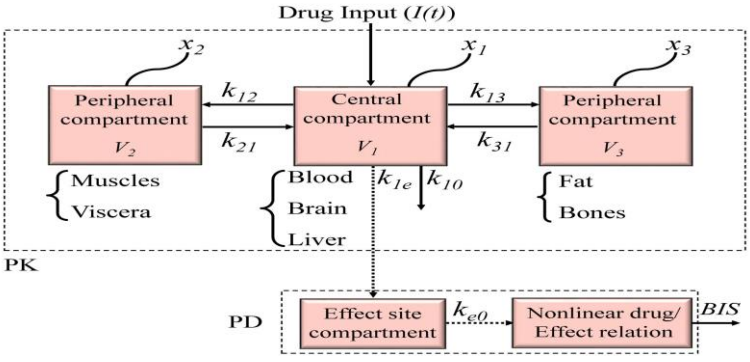

Fig. 4 Three-Compartmental model of the patient

The speed at which the drug moves from i-th to j-th compartment is represented by the constants kij (min-1), while The pace at which the drug is broken down through metabolism is indicated by the constant k10, and the volume of the first compartment is denoted by V1.

2) Pharmacodynamic models

The two components of the typical pharmacodynamic (PD) model, as shown in Figure 4, are utilized to establish the relationship between a drug's concentration and its effects on the body. The first component of the standard PD model is the "effect-site," which was introduced by [18] to account for the delay between the drug's concentration and its effect. For anesthesia, it is assumed that the impact of the effect-site compartment is insignificant since it is much smaller than the central compartment [18]. The effect-site concentration and plasma concentration can be related using the following equation in steady-state:

$$C_e=x_e=k_{1e}x_1 - k_{e0}x_e \quad (4)$$

The variables k_{e0} and k_{1e} are both constants, and x_e represents the quantity of the drug present in the effect compartment. It is assumed that the rate of drug intake and elimination from this compartment remains constant, with k_{e0} serving as the constant rate of both processes (for example, propofol has a k_{e0} of 0.456, which is equal to k_{1e}) [19].

C . Control

Both control engineers and clinicians have been interested in control applications for general anesthesia for several decades. During this time, various methods have been proposed to automate the process to different degrees [20]. The computation of drug infusion rates in the majority of systems can be classified into one of three methods: manual, open-loop feed-forward, or closed-loop controllers. The conventional method, as seen in figure 6, is the manual system, which entails an anesthesiologist setting the final Depth of Anesthesia (DoA) or Hypnosis (DoH) value and modifying drug dosages based on monitoring the patient's condition [21]. However, the effectiveness of this technique is reliant on the anesthesiologist's proficiency and is not dependable in critical scenarios, such as unexpected incidents during surgery.

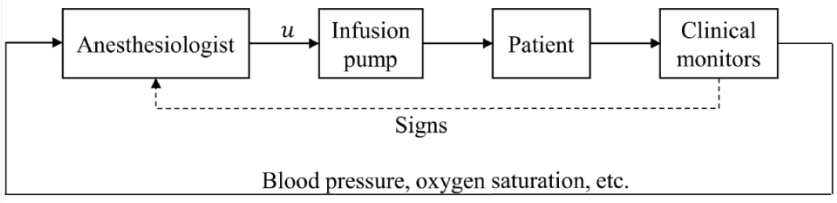

Fig. 5 Manual control of anesthesia

In 2003, the development of TCI systems marked a significant stride towards completely automated anesthesia. The Diprifusor system was the first introduced TCI pump for propofol and subsequently additional TCI systems have been offered by multiple manufacturers. Consequently, TCI systems have become the standard method for dispensing anesthetic drugs in clinical settings [22]. According to our classification, the operational mode of TCI systems is that of open-loop feed-forward controllers, as demonstrated in Figure 6, and rely on an anesthesiologist's assessment of the patient's status, as well as The PK/PD model's output, to determine the correct medication dose and infusion duration. In practical

terms, the target drug concentration was set by the anesthesiologist and the infusion rate was calculated by the TCI system and this value will be transmitted to the infusion pump. While TCI is utilized within several countries and offers certain benefits compared to anesthesia systems that are operated manually, its efficacy is still dependent on the anesthesiologist's proficiency and lacks the capacity to determine the required infusion rate to meet the patient's present requirements. Due to the absence of instantaneous feedback in TCI, its effectiveness hinges on the precision of the patient model and is vulnerable to interruptions arising from stimulation during surgery and the synergistic effects of hypnotic and opioid drugs [23].

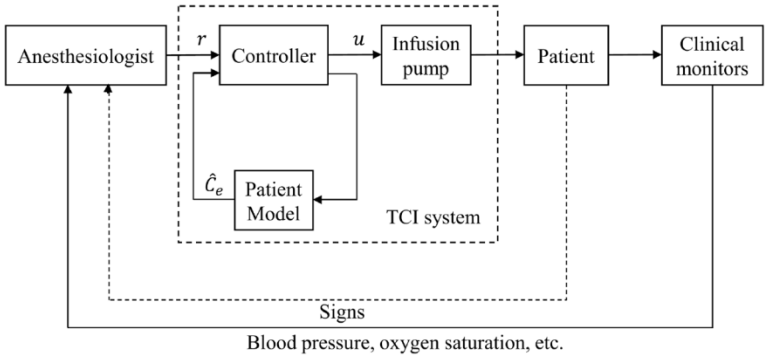

Fig. 6 Open-loop feedforward control (TCI)

The most advanced type of controllers, illustrated in Figure 7, are the closed-loop controllers. They consider both the clinical metrics employed by anesthesiologists in manual and TCI techniques, as well as the patient's individual physiological parameters. These physiological parameters, such as EMG, EEG, ECG, and BIS, can be obtained from advanced monitors that display the patient's measurements. Closed-loop controllers use feedback control to continuously modify the infusion rate or target concentration, taking into account the patient's physiological parameters, rather than depending on an anesthesiologist However, anesthesiologists are still required to establish the desired level of anesthesia or hypnosis and assess the patient's condition using clinical metrics. This was previously discussed in Section III-A.

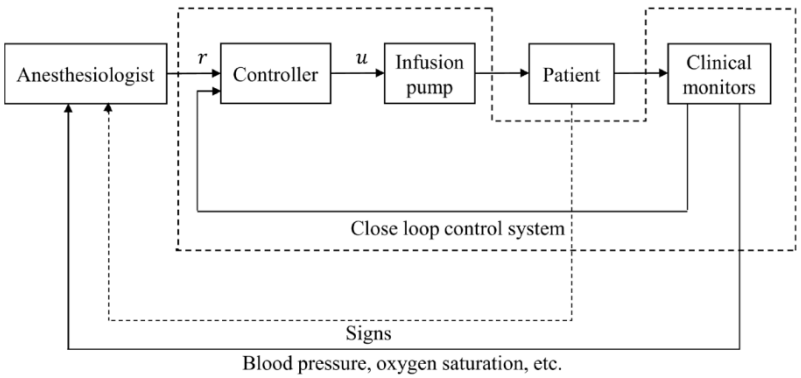

Fig. 7 closed-loop control system

By using fully automated systems for administering anesthesia, anesthesiologists may benefit from a reduced workload, which could potentially help prevent problems caused by distractions and fatigue. Additionally, continuous monitoring provided by these systems can enhance patient safety and potentially lead to decreased drug dosages, quicker postoperative recuperation, and a reduction of drug-induced side effects. Hence, it's possible that fully automated systems may surpass manual infusion dosing in the future [24].

Figure 8 demonstrates two separate techniques for executing closed-loop controllers in anesthesia. The first method (Fig. 8a) involves identifying anesthetic infusion rates directly and sending control signals to the infusion pump, such as [25] The second method (Fig. 8b) adjusts the target value for a downstream Target-Controlled Infusion (TCI) system continually, which in turn controls the infusion pump's rate, such as [26] Since the second approach can be seen as a particular case of the first method, the first or direct approach is less limiting and may be more appropriate for control system design, as it allows for the replacement of TCI dynamics with any efficient algorithm.

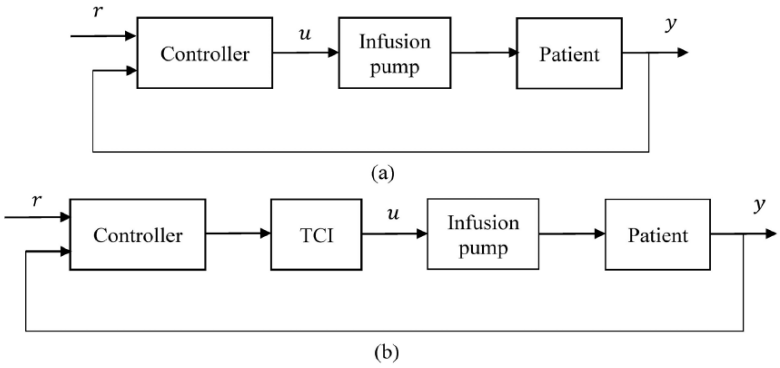

Fig. 8 Anesthesia Closed-loop control architectures

Automating anesthesia requires three essential components: a patient model, a measurement system comprising of sensors or monitors, and a controller. The performance of both individual components and the overall system can be significantly affected by one another. By enhancing the precision and accuracy of mathematical models, it is possible to develop controllers that can offer superior infusion rate. Additionally, as Measurement equipment with greater precision and the parameters of the physiological model are determined with greater accuracy, controllers can receive more and higher-quality feedback, therefore enhanced drug infusion can be obtained. It is important to recognize that the quality of monitoring has a direct impact on the performance of the controller during implementation. Although Sections III-A and III-B have concentrated on monitoring and modeling, designing the controller is still one of the most significant obstacles in automating anesthesia, and several notable approaches will be explored. To develop automated anesthesia control systems, researchers and control engineers have investigated numerous control techniques, including PID, MPC, fuzzy-logic, adaptive, and neural networks, Furthermore, these controllers can be used in combination with one another. The general structure of closed loop control outlined in Fig. 9. Detailed overviews of controller designs can be obtained in [27], [28], [29].

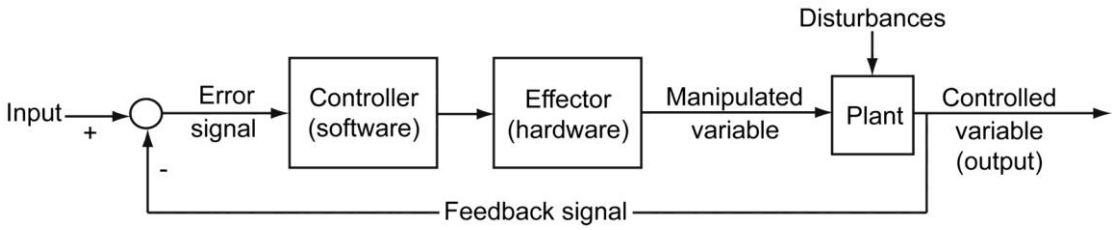

Fig. 9 Anesthesia closed-loop control

Although the majority of recent studies on physiological closed-loop control of anesthesia have concentrated on intravenous anesthesia, there have been some investigations into the utilization of inhalational anesthesia [30]. Utilizing inhalational anesthesia provides an advantage in that it allows for the measurement of end-tidal gas levels, which can monitor levels of drugs in both the brain and vessel-rich group (VRG) under conditions of stability. Nonetheless, In situations that are characterized by constant change, such as during the initial absorption and emergence, these sensors may not provide accurate estimates of VRG concentration [31]. In order to tackle this problem, certain researchers have created mathematical models to estimate concentration and have studied closed-loop control of inhalational anesthesia through simulations and clinical studies using model predictive control [32][33]. Those who wish to gain a deeper understanding of inhalational anesthesia in terms of modeling and controlling can consult the vast array of literature available, including [34].

This section will analyze the controllers that are commonly utilized in closed-loop anesthesia control, It will also discuss the current advancements and persistent obstacles associated with each of these methods.

1) PID controller

This controller is widely adopted in industrial settings because of its uncomplicated mathematical formulation, straightforward gain tuning techniques, and versatile functionality. Over the past two decades, several clinical and simulation studies have utilized PID-based controllers in automated anesthesia, Overall, the findings of these studies suggest that PID control has the potential to be beneficial in closed-loop anesthesia management. One example of a commonly used PID controller in anesthesia is the Laplace domain transfer function [35].

$$\frac{U(s)}{E(s)} = k_p\left(1 + \frac{1}{sT_i} + T_d s\right)\frac{1}{(T_f s+1)^2} \qquad (5)$$

The equation presented here is a PID controller that is utilized in anesthesia, The equation presented here is a PID controller that is utilized in anesthesia, In the Laplace domain, U(s) represents the control signal, while E(s) denotes the error signal. This controller consists of various parameters such as k_p which refers to the proportional gain, Ti denotes integral time-constant, Td denotes the derivative time-constant, and Tf represents the time-constant of a second-order filter, which aids in reducing measurement noise. Earlier investigations have demonstrated that PID controllers can effectively follow desired anesthesia levels, such as BIS values. Nonetheless, both anesthetists and control engineers

acknowledge that the fundamental PID algorithm has significant drawbacks, as it lacks resilience and adaptability and performs inadequately in the face of noise and physiological fluctuations. In closed-loop anesthesia control, the straightforward PID method exhibits insufficient disturbance rejection capability, primarily because of inter-patient variability, which can result in undesirable oscillations in the BIS response. Moreover, the integral control element may undergo windup during the induction phase. As a result, recent research endeavors to tackle these issues and attain comparable performance to that of the more sophisticated controllers.

2) Model predictive control

The MPC is an effective control method that is both optimal and robust. The purpose of its design is to effectively manage constrained systems by optimizing controller actions and predicting system outputs, thereby ensuring resistance to noise and disturbances. Medical systems, particularly closed-loop anesthesia control, have seen the usefulness of MPC and related techniques like Generalized Predictive Control (GPC), as evidenced by recent clinical and simulation results [36]. As a result, control engineers are now more motivated to create MPC controllers capable of managing the intricate and nonlinear nature of closed-loop anesthesia control.

The computational complexity of solving online optimization problems restricts the real-time applications of standard MPC. The Multi-Parametric Model Predictive Control (mp-MPC) technique can overcome this limitation by resolving optimization problems through offline methods on analytical functions rather than numerical solutions [37]. In addition, the combination of sophisticated state estimation strategies such as Kalman filtering and Moving Horizon Estimation (MHE) with MPC can enhance the capability to reject BIS noise and surgical disturbances. Simulation studies suggest that Moving Horizon Estimation (MHE) yields enhanced precision and less overtake than Kalman filtering [38]. Studies have indicated that by integrating event-driven inputs and incorporating state output correction mechanisms into MPC, its capacity to withstand noise can be improved and the amount of anesthetic drugs given can be reduced [39]. By estimating pharmacodynamic parameters in real-time, determining the gradient of the linearized Hill equation for every individual time interval, and implementing offset-free and state output correction strategies, MPC has the ability to tackle both inter-patient and intra-patient variability [33]. Utilizing piecewise linear PK/PD models can tackle the challenge of nonlinearity in the pharmacodynamic (PD) model, which is a vital aspect of closed-loop anesthesia control. To achieve a more precise linear approximation of the hill function using above mentioned technique we require dividing the hill function into multiple linear segments [40].

$$Ce(t) = EC50 \left(\frac{E_0 - BIS(t)}{E_{max} - E_0 + BIS(t)}\right)^{\frac{1}{\gamma}} \quad (6)$$

One frequently used approach to handle the nonlinearity present in the anesthesia system by applying multiplication between the inverse of the Hill function and both the input command and feedback signal.

3) Adaptive control

Controllers that can adapt to systems that have uncertain or unknown parameters are widely utilized. These controllers employ algorithms that enable them to retune or restructure the controller while it is operating, which is known as online adaptation [41]. Given the significant (and potentially time-varying) uncertainties in the anesthesia PK/PD model and the varying coefficients across patients, adaptive controllers show potential in improving anesthesia regulation and parameter estimation for the PK/PD model. Direct adaptive controllers modify their controller gains directly instead of relying on an internal model, and are considered as adaptive controller. The adaptive PID control algorithm is an instance of direct adaptive control that allows adaptive anesthesia control without relying solely on the PK/PD model [42].

Various types of adaptive feedback controllers, including the model reference adaptive controller (MRAC), can be employed to regulate anesthesia. However, using conventional models, MRAC controllers have not exhibited significant performance enhancements compared to non-adaptive techniques. An alternative method is to use fractional order models to implement MRACs. The use of these models in research has shown the efficacy and resilience of the resultant fractional order model reference adaptive control (FOMRAC), that mitigate the effects of time delays in the anesthesia system [43]. Moreover, L1-adaptive techniques can attain more rapid adaptation than MRAC and have displayed satisfactory efficiency and robustness among different patients [44]. System identification methods can be employed to reduce the order of patient models and enhance performance beyond conventional L1-adaptive control. Moreover, L1-adaptive controllers can facilitate safe transitions between manual and automated closed-loop operation modes [45].

4) Fuzzy logic control

The use of fuzzy modeling and control can provide benefits in the closed-loop control of anesthesia due to the limitations of compartmental models in accurately representing the complexities of the human body and their susceptibility to variations in the various parameters that govern its system. The practical application of fuzzy logic has shown effectiveness in all three key component of anesthesia, which are hypnosis, analgesia, and immobility. Detailed analysis of these implementations can be referenced in [46] and [47]. The primary advantage of employing fuzzy logic in anesthesia lies in its capacity to create patient models by clustering actual patient data without requiring any prior understanding of the underlying physiology. The majority of fuzzy anesthesia systems utilize conventional fuzzy sets (type-1) where the membership values are precise values falling within the range of [0, 1]. Nonetheless, certain systems implement type-2 fuzzy sets, wherein the membership values of each element are fuzzy sets in their own right, ranging within [0, 1] [48]. A notable difficulty that arises when working with fuzzy models involves determining the most appropriate membership function (MF) for these fuzzy sets that fall within the [0, 1] range. Optimization algorithms such as genetic and neural network can be frequently utilized To improve efficiency and fine-tune the parameters of type-2 fuzzy sets, such as the footprint of uncertainty (FOU), centroid, and scaling factors [49].

To devise fuzzy control laws for anesthesia, a collection of rules is gathered by soliciting the viewpoints of anesthesiologists regarding the most suitable remedial measures to undertake in different scenarios. Using these rules, a closed-loop system is developed that can emulate the proficiency of

anesthesiologists in manually administering infusions. Despite the incorporation of rules, fuzzy-logic controllers have showed inadequate efficiency, necessitating the use of optimization algorithms. Incorporating these optimization algorithms enhance the ability of the fuzzy controller to adjust to the variations within and between patients [50]. Fuzzy-logic controllers are commonly modified to become self-organizing controllers having the ability to adjust according to alterations within the system. Nevertheless, these controllers may generate steady-state error when utilized in bolus-type therapy. To address this issue, a basic fuzzy-logic controller can be utilized during bolus treatment, with the controller being switched to a self-organizing fuzzy-logic type once the system is functioning in proximity to the target set-point [51]. As previously mentioned, a genetic algorithm can be employed to optimize the fuzzy-logic model [46]. Type-1 sets serve as the foundation for most fuzzy-logic controllers, but their inability to manage model uncertainties may produce steady-state error. This limitation can be addressed by employing type-2 fuzzy sets [52]. Furthermore, while fuzzy neural network controllers are capable of handling uncertainties in anesthesia, their effectiveness is restricted when using type-1 fuzzy sets. To overcome this issue, type-2 fuzzy neural network controllers can be utilized. While self-organizing type-2 fuzzy-logic controllers can compensate for control uncertainties, their efficacy may be diminished by signal noise and dynamic uncertainties, such as variations in the pharmacodynamic and pharmacokinetic systems [48]. As a result, to enhance performance in the presence of uncertainties, fuzzy-logic controllers can be integrated with other control schemes like model predictive control. Although genetic algorithms can be employed to determine the optimal membership function for the self-organizing type-2 fuzzy-logic controller, this approach may result in increased error in environments that are free of noise [53].

IV. Challenges to automated anesthesia

When creating a drug infusion controller, specific limitations must be considered throughout the design and simulation stages. It is crucial to recognize that there exists a highest effective dosage for every drug, indicating that administering larger doses will not yield any further advantages to the patient. Secondly, since the infusion rate is regulated by the control signal, it must stay positive and within the infusion pumps' range to prevent the drug from being extracted after the infusion. Thirdly, it should be noted that high doses administered over a short period can be harmful to the human body and may result in damage to the organ systems [54]. To prevent potential harm to the body's organ systems, it is advisable to maintain lower infusion rates. Balancing the adverse effects caused by fast infusion with the need to achieve the desired BIS value within a specific timeframe is crucial in determining the appropriate drug infusion rates. According to literature, the recommended time frame for current surgical procedures is approximately 15 minutes [55]. However, simulation studies have been able to achieve shorter timeframes, such as 4-8 minutes, as reported in the literature [35].

Lastly, ensuring the effectiveness of the designed anesthesia controller in the presence of inter-patient and intra-patient variability is crucial. Inter-patient variability refers to differences in physiological parameters between individuals, as each patient may respond differently to drugs, while intra-patient variability refers to changes in physiological parameters that occur within a patient over time. The main difficulty with inter-patient and intra-patient variability in closed-loop control of anesthesia is that these

variations can significantly affect the dynamics of the system, which makes it challenging to develop a controller with consistent performance across a broad range of patients. In addition to the mentioned constraints, the design of the anesthesia control system should also take into account the impact of disturbances and noise that may arise from sources like surgical stimulations and poor signal quality. The modeling and controller design process must address these factors to ensure accurate and reliable control of anesthesia. Clinicians and control engineers are currently exploring ways to mitigate the impact of surgical stimulations, which are considered one of the most difficult disturbances to manage in the context of system modeling and controller design.

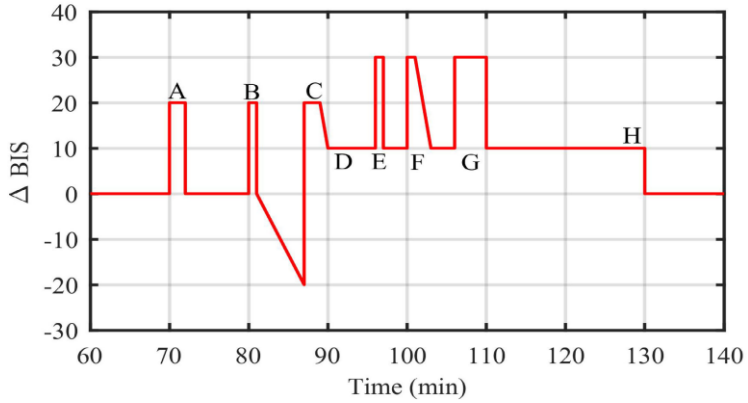

Fig. 12 Typical profile for surgical stimulation (adapted from [56]).

Addressing various types of disruptions and interference, such as low-quality signals and stimuli during surgery, is crucial for ensuring accurate anesthesia closed-loop control. Surgical stimulations can significantly impact the BIS index, as illustrated in Figure 12, which shows a timeline of BIS index variations during a surgical procedure. The timeline comprises various stimuli, including but not limited to, arousal caused by laryngoscopy/intubation, surgical incision, sudden and persistent surgical stimulation, and high-amplitude short-term stimulations. However, the accuracy and reliability of sensing techniques for monitoring depth of anesthesia (DoA) can be affected by various factors, including demographic characteristics, EMG signals, and interactions with other substances like NMB drugs or opioids, as reported in recent studies [56][57][58]. Accurate closed-loop control of anesthesia requires the development of more precise and robust sensing technologies, due to the presence of various stimuli that can cause disruptions and interference, such as low-quality signals and stimuli during surgery. The research suggests that utilizing an anesthetic PCLC device may result in achieving the intended BIS value without meeting the required level of DoA, which could potentially lead to anesthesia awareness. Automated anesthesia encounters obstacles from sensing noise, measurement errors, and sensing delays, even when the sensing paradigm accurately represents the DoA.

V. Future vision for automated anesthesia

As previously stated, closed-loop control of anesthesia commonly utilizes four types of controllers: PID, MPC, adaptive controller, and fuzzy-logic controllers. However, other types of controllers, such as nonlinear H-infinity controllers, robust and robust deadbeat controllers, observer-controllers, sliding mode controllers, non-overshooting tracking controller, and other nonlinear controllers, have also been explored for their potential use in anesthesia [59]. These studies have utilized various performance metrics, including performance error (PE), least obtained BIS value (BIS-NADIR), overshoot, undershoot, settling time, integrated absolute error (IAE), median performance error (MDPE), median absolute performance error (MDAPE), total variation (TV), and WOBBLE (an indicator of fluctuations in the response over a period of time), to compare and evaluate the efficacy of these control strategies, to identify the most suitable type of controller for anesthesia control. Most of these controllers have shown acceptable performance from a control systems perspective. Recent research has also investigated safety mechanisms for closed-loop control of anesthesia [60].

Because anesthesia is crucial and the regulatory restrictions that ensue, none of the controllers have received full clinical approval for use in a closed-loop anesthesia system [61]. Moreover, considering the presence of intra- and inter-patient variability, surgical disturbances, and nonlinear dynamics, none of the four controllers mentioned can adequately address the complex issues associated with anesthesia on their own. Recent studies (cited in [62], [63]) suggests that a promising approach for enhancing the performance of closed-loop anesthesia and achieving satisfactory simulation outcomes is to combine these controllers while optimizing their respective strengths. Enhanced physiological models that account for the interactions between multiple organ systems, physiological parameters, and clinical signs across various subjects and surgical scenarios can facilitate building automated anesthesia systems that can attain widespread regulatory authorization. Developing anesthesia models that include all three modes of anesthesia and analyzing simulation results at an early stage are essential to increase assurance regarding the safety and effectiveness of control algorithms. Collaboration between clinicians, anesthesiologists, mathematicians, and control engineers is necessary to construct anesthesia models that are pertinent to control, have lower complexity, and can account for differences between patients and within the same patient. Automated anesthesia could benefit from the advancement of clinical monitoring techniques aimed at reducing measurement noise and time delays significantly, as well as creating techniques to measure particular facets of anesthesia. One way to improve automated anesthesia is by developing techniques for clinical monitoring that can reduce measurement noise and time delays and quantify specific aspects of anesthesia. For instance, measuring the depth of anesthesia could enable the development of reliable metrics using multimodal monitoring through sensor fusion. Measuring drug concentration in the effect compartment could be a viable solution for addressing challenges caused by the nonlinear pharmacodynamics of anesthesia. Replacing or supplementing BIS values with drug concentration measurements in the effect compartment is a potential solution to address the challenges arising from the nonlinear pharmacodynamics of anesthesia, and it may eliminate the need for corresponding nonlinear model equations. However, it is crucial to acknowledge that current monitoring technologies have constraints, and until a dependable, real-time measure of the direction of arrival (DoA) is identified, it is not advisable to implement fully automated anesthesia. To account for potential variations in drug interactions and patient responses, moderate levels of automation (LOA) in PCLC anesthesia devices are preferred over fully autonomous anesthesia. Research aimed at identifying

the most effective combination of control strategies can result in the creation of practical controllers that perform well in real-world settings, despite limitations on drug infusion, variability among patients, disturbances, noise, and nonlinearities. Meeting safety and regulatory requirements is also crucial. Table 1 provides an overview of the latest results in closed-loop control of anesthesia.

Table 1. Control techniques in anesthesia.

#	Author	Year	Control approach	Controlled variable	Measured variable	Simulation /trial	Ref
1.	Schiavo et al.	2022	PID	Hypnosis/Analgesia	BIS	trial	[64]
2.	Sanches et al.	2022	MPC/MHE	Hypnosis	BIS	simulation	[65]
3.	Sun et al.	2022	LRM	Hypnosis	IES	trial	[66]
4.	Schamberg et al.	2022	PID	Hypnosis	PSI	simulation	[67]
5.	Oshin	2022	MPC	Hypnosis	BIS	simulation	[68]
6.	Yun et al.	2022	RL	Hypnosis/Analgesia	BIS	simulation	[69]
7.	Pawłowski et al.	2022	MPC	Hypnosis	BIS	simulation	[70]
8.	Ribba et al.	2022	RL	Hypnosis	BIS	simulation	[71]
9.	Pawłowski et al.	2022	MPC	Hypnosis/Analgesia	BIS	simulation	[72]
10.	Jarrett et al.	2022	BCLC	Hypnosis	BIS	simulation	[73]
11.	Calvi et al.	2022	RL	Hypnosis	BIS	simulation	[74]
12.	Jamali et al.	2021	ANFIS	Hypnosis	BIS	trial	[75]
13.	Kumar et al.	2021	FL	Hypnosis	HR/BP	simulation	[76]
14.	Maxim et al.	2021	MPC	Hypnosis/HD	BIS	simulation	[77]
15.	Schiavo et al.	2021	PID	Hypnosis/Analgesia	BIS	simulation	[78],[79],[80],[81]
16.	Kagami et al.	2021	PID	Hypnosis/Analgesia	BIS	simulation	[82]
17.	Ntouskas et al.	2020	MPC	Hypnosis	BIS	simulation	[83]
18.	Gonzalez et al.	2020	MPC	Hypnosis/Analgesia	BIS	trial	[84]
19.	Schamberg et al.	2020	RL/PID	Hypnosis	BIS	simulation	[85]
20.	Veerakumar et al.	2020	PID	Hypnosis	BIS	simulation	[86]
21.	Jamali et al.	2020	ANFIS	Hypnosis	BIS	trial	[87]
22.	Eskandari et al.	2020	MPC	Hypnosis/Analgesia	WAV	simulation	[24]
23.	Penaranda et al.	2020	FL	Hypnosis/Analgesia	PSI	trial	[88]
24.	Savoca et al.	2019	MPC	Hypnosis/Analgesia	BIS/MAP	simulation	[89]
25.	Patel et al.	2019	MPC	Hypnosis	BIS	simulation	[90]
26.	Wei et al.	2019	T2-SOFLC	Hypnosis	BIS	simulation	[91]
27.	Liang et al.	2019	PID	Hypnosis	BIS	simulation	[92]
28.	Padmanabhan et al.	2019	RLBAC	Hypnosis	BIS	simulation	[93]
29.	Van Heusden et al.	2019	PID	Hypnosis	BIS	trial	[94]
30.	Khodaei et al	2019	ANFIS	Hypnosis	BIS	simulation	[60]
31.	Abood et al.	2019	ASMC	Hypnosis	BIS	simulation	[95]

32.	Merigo et al.	2018	PID	Hypnosis	BIS	trial	[96]
33.	Patel et al.	2018	PID	Hypnosis	BIS	trial	[97]
34.	Yu et al.	2018	T2-SOFLC	Hypnosis	BIS	simulation	[53]
35.	Navarro et al.	2018	AC	Hypnosis	BIS	simulation	[97]
36.	Samira et al.	2018	FL	Hypnosis	HR/BP	simulation	[98]
37.	Copot et al.	2018	PID	Hypnosis	BIS	simulation	[99]
38.	Mendez et al	2018	FL	Hypnosis	BIS	trial	[23]
39.	Savoca et al.	2018	MPC	Hypnosis/Analgesia	MAP/BIS	simulation	[100]
40.	Taheriyan et al.	2018	T2-FLC	Hypnosis/MR	MR/BP		[101]
41.	An et al.	2017	PID	Hypnosis	BSP	simulation	[102]
42.	Zaouter et al.	2017	RBA	Sedation	BIS/RR/SpO2	trial	[6]
43.	West et al.	2017	PID	Hypnosis/Analgesia	WAV	trial	[103]
44.	Merigo et al.	2017	PID	Hypnosis	BIS	simulation	[104]
45.	Pawlowski et al	2017	MPC	Hypnosis	BIS	simulation	[39]
46.	Zaouter et al.	2017	PID	Sedation	BIS	trial	[105]
47.	Nascu et al.	2017	MPC	Hypnosis	BIS	simulation	[106],[55]
48.	Ingola et al.	2017	MPC	Hypnosis	BIS	simulation	[40]
49.	Copot et al.	2017	FOPI	Hypnosis	BIS	simulation	[30]
50.	Padula et al.	2017	PID	Hypnosis	BIS	simulation	[35]

PID= proportional integral derivative, MPC= model predictive control, BIS= bispectral index, MHE= moving horizon estimation, IES= isoelectric suppression, LRM= logistic regression model, PSI= patient state index, RL= reinforcement learning, FL= fuzzy logic, BCLC= Bayesian closed-loop controller, ANFIS= adaptive neuro-fuzzy inference system, T2-SOFLC= type-2 self-organizing fuzzy logic controllers, HR= heart rate, BP= blood pressure, MAP= mean arterial pressure, RR= respiratory rate , BSP= burst suppression probability, SpO2= oxygen, saturation, WAV= wavelet-based anesthetic value, MR= Muscle relaxation, FOPI= fractional order proportional integral controller, ASMC= adaptive sliding mode controller, RBA= rule based algorithm, AC= adaptive control, RLBAC= reinforcement learning based adaptive control, HD=hemodynamic.

According to data in table 1., The considered control approaches in anesthesia (2017-2022) are summarized in figure 13.

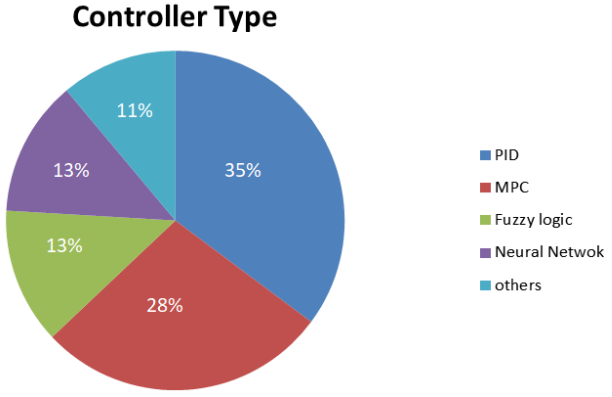

Fig. 13 controller type used in table.1 (2017-2022)

VI. CONCLUSION

Despite significant progress in both physiology and technology, closed-loop control of anesthesia titration remains in the experimental phase and has yet to become a routine clinical practice. The complexity of the anesthesia process, which requires integrated regulation of all anesthesia-related drugs (such as hypnosis, analgesia, neuromuscular blockade, hemodynamics, and respiratory dynamics), and the current level of control strategies' advancement are not yet sufficient for inclusion in standard hospital use. However, in-silico simulations and clinical trials are currently underway, and they have shown encouraging outcomes in terms of patient safety, expert support, and economic impact. Hence, it is only a matter of time before a significant development transpires in this domain. Achieving accurate drug infusion requires the development of medical cyber-physical-human systems that can integrate context awareness, device communication, human-machine cooperation, control, and optimization algorithms. Regulatory approval, clinical validation, and ethical concerns also need to be addressed to ensure the safe and effective implementation of this technology in clinical practice.

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