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Closed-Loop Control of Anesthesia: Survey on Actual Trends, Challenges and Perspectives

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ABSTRACT Automation empowers self-sustainable adaptive processes and personalized services in many industries. The implementation of the integrated healthcare paradigm built on Health 4.0 is expected to transform any area in medicine due to the lightning-speed advances in control, robotics, artificial intelligence, sensors etc. The two objectives of this article, as addressed to different entities, are: i) to raise awareness throughout the anesthesiologists about the usefulness of integrating automation and data exchange in their clinical practice for providing increased attention to alarming situations, ii) to provide the actualized insights of drug-delivery research in order to create an opening horizon towards precision medicine with significantly improved human outcomes. This article presents a concise overview on the recent evolution of closed-loop anesthesia delivery control systems by means of control strategies, depth of anesthesia monitors, patient modelling, safety systems, and validation in clinical trials. For decades, anesthesia control has been in the midst of transformative changes, going from simple controllers to integrative strategies of two or more components, but not achieving yet the breakthrough of an integrated system. However, the scientific advances that happen at high speed need a modern review to identify the current technological gaps, societal implications, and implementation barriers. This article provides a good basis for control research in clinical anesthesia to endorse new challenges for intelligent systems towards individualized patient care. At this connection point of clinical and engineering frameworks through (semi-) automation, the following can be granted: patient safety, economical efficiency, and clinicians' efficacy.

INDEX TERMS Closed-loop control, drug-delivery control, anesthesia, (semi-)automated anesthesia delivery, cyber physical medical systems, decision support systems, adaptive control.

I. INTRODUCTION

Is anesthesia management prone to error? Can one believe that such a standard procedure is applied optimally as a familiar routine OR, on the contrary, with major risks due to patient inter- and intra-variability? Either way, there is room for improving the anesthesia optimization and decrease the risks for the patients.

Driven by societal challenges, the fast progress of advanced technology has been finding scalability to many applied industries. The fourth industrial revolution's effects on the future of health and well-being are translated into the emerging extension named Health 4.0 [1]. This process is empowered by adaptable cyber physical systems (CPSs), that integrate computation and physical entities through communication infrastructure. Based on dynamical context-awareness at different scales in the physical world, CPSs allow semi-independent or independent execution of advanced tasks [2]. So, the fusion of technologies across physical, digital and biological areas resides at the core of health sector performance and has a transformative impact on drug delivery control systems. While close collaboration

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between engineers and clinicians are witnessing spectacular growth, the essential role of drug control and modelling in meeting one of the critical societal challenges (healthcare) is envisaged across the research community [3].

CPSs have been on the rise in the medical field because of their potential to project a transformative impact on medicine. In such a changing environment, the analysis of Big (healthcare) data seized in real-time achieves precision and individualization towards the patient's care, guiding specialists' decisions based on context-awareness approach. The benefits of the combination between a monitoring system, a controlling software, and a communication channel have been also recognized in the operation room for surgical procedures or for anesthesia delivery [4], [5], such that automated administered intravenous anesthesia had better results over manual and target controlled infusion (TCI) techniques [6]. Effective control of total intravenous anesthesia (TIVA) is one of the most important issues in the field of surgery, because millions of people worldwide undergo operations daily. Besides, inadequate intraoperative anesthesia or treatment of postoperative pain can cause post-operatory complications. Unintended intraoperative awareness with recall is a potential complication of under-dosing that continues to occur during TIVA [7]. An important role to maintain the positive balance is played by computer-controlled infusion systems, whereas medicine and engineering go hand-in-hand for better results [8]. The decision actions must tackle: increased clinical workload, different anesthesia infusion practices to deal with large interpatient variability (correlated with the doctor's expertise level), repeatedly use of constant drug infusion rate (slightly overdosing). A standardized high-quality anesthesia decision support systems (DSS), reduction of post-operative effects, individualized and adapted drug infusion, and robust maintenance of target values are the main factors motivating automation in anesthesia administration.

While a hot topic, autonomous systems in anesthesia have been deployed with considerable success in research, as reviewed by Zaouter *et al.* [9], but limited in its implementation in hospitals in integrated medical cyber physical systems (MCPSs). Over the past decades, research groups have focused on multiple control strategies, patients states monitors, adaptive optimization algorithms, drugs interactions, modelling approaches, and more other components of the complex process towards anesthesia control. The new technology and methodologies brought by control systems could change the way people receive anesthesia. It would enable personalized services that are more responsive to patient's state, offering optimized drug doses and preventive surgical approaches that ultimately create a more sustainable patient peri- and post-anesthesia care.

The main contribution of this survey is the presentation of the most recent closed-loop anesthesia systems in the actual technological, societal, and economical context. The complex paradigm of anesthesia regulation is described from the viewpoint of control optimization, modelling, and feedback. Moreover, this article discusses the social and economic value creation through transfer of the innovative knowledge and technology in anesthesia automation. The objectives of the paper are addressed to both anesthesiologists and researchers. In order to raise awareness between anesthesiologists, it is motivated the potential of control integration in their clinical practice as decision support systems, and not as their replacement. On the other hand, a broad overview of the actual trends on closed-loop anesthesia control is presented. However, adoption of automated systems is not any more a challenge in many domains, but healthcare and mostly in anesthesia still miss control integration in the patient care.

The structure of the paper is further presented. Next section introduces the parallelism between everyday clinical practice in open-loop versus closed-loop delivery of anesthetics. Based on this comparison, the third section presents the theoretical aspects needed to be met in anesthesia control systems, by defining the particular specifications from the control viewpoint. The overview of control strategies are referred with recent publications in the fourth section, while the opportune research perspectives driving innovations are addressed in the final section.

II. ANESTHESIA: OPEN- VS CLOSED-LOOP

General anesthesia requires adequate balance between hypnosis, analgesia, and neuromuscular blockade (NMB) [10], while maintaining the other patient's parameters in the safe range. Technological monitoring assures detection and alarm of complications, but clinical observation is essential based on anesthetist's skills and experience [11]. Appropriate monitoring devices recommended in anesthetic standards are summarized in Fig. 1 for depth of anesthesia (e.g., processed electroencephalography, newly researched pain monitors, peripheral neuromuscular transmission monitor), for hemodynamics (pulse oximeter, electrocardiography, blood pressure), for respiratory dynamics (oxygen supply, pulse oximeter, auscultation, clinical observation), and for temperature [10]. In this manner, the monitors supplement clinical observation in order to achieve optimal drug doses for anesthesia-hemodynamics-respiratory management. Fig. 1 endorses the integration of a cyber-physical-human system (CPHS) in the clinical practice. Through its objective, the context-aware control system can guide optimal infusion rate and can release the anesthesiologist from its repetitive tasks, such as continuous assessment of patient state or implementation of well-defined international standards. Moreover, the pandemic outbreak COVID-19 adds specific risks paired with infected patients that need to be tackled (e.g. acute cardiac injury and arrhythmia) [12]. While computer-based drug delivery can handle routine situations for anesthesia and hemodynamics maintenance, the medical specialists can focus on high rated tasks. Consequently, a sedation-hemodynamic regulation during general anesthesia can achieve its potential both in operating rooms and intensive care units (ICU).

Delivery of anesthesia involves a repeated cycle of assessing the patient's state and using this data to adjust medication.

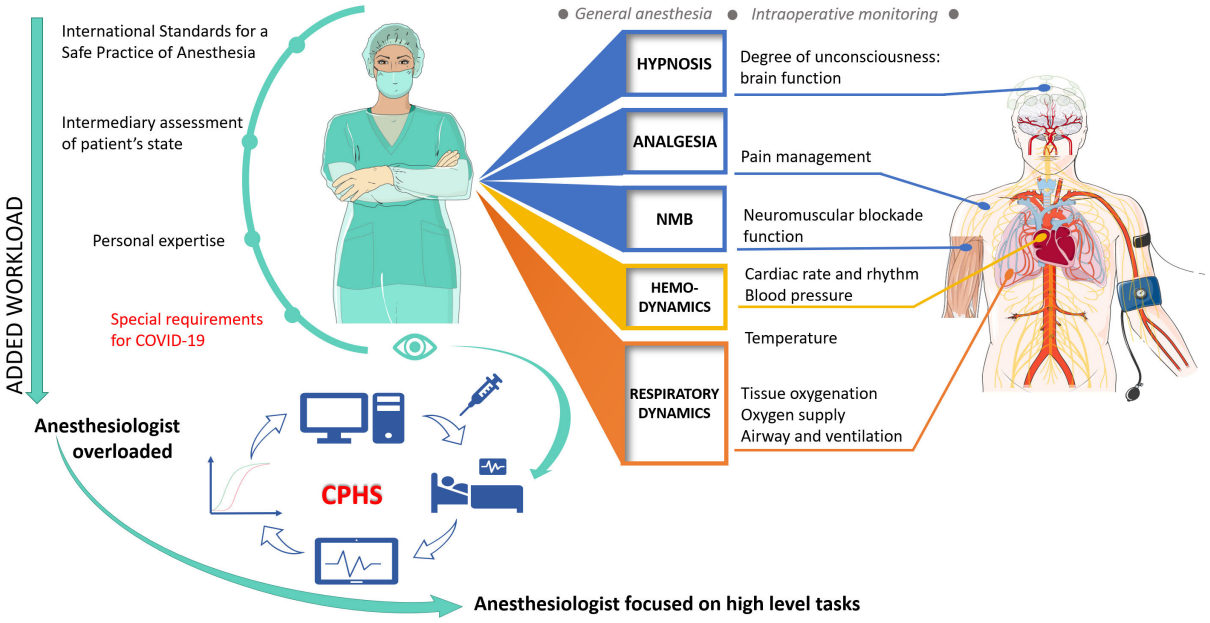

FIGURE 1. Clinical care paradigm for patient's state monitoring during general anesthesia and the potential of a hybrid CPHS with medical human in the loop.

Nowadays, computer-controlled drug delivery is done by open-loop target-controlled infusion (TCI) systems, the first step toward automation of drug delivery. TCIs maintain a constant infusion rate of the anesthetic, modeled using pharmacokinetics principles for the target effect-site or plasma concentrations dictated by the practitioner [13]. However, the anesthesiologist is implied in the control loop by selecting the initial target doses or concentrations and adjusting them accordingly to the peri-operative evaluation of the patient's state. The effect of the drugs on each patient is assumed by the clinicians based on monitoring devices, clinical expertise, and previous experience. While this strategy is manually closed by the anesthesiologist, closed-loop control systems use direct measurements from depth of anesthesia monitors in order to automatically adapt the infusion rates. The measured response of the patient is used as feedback for the controller. Then, the anesthesiologist receives other high-level roles, such as manually monitoring of specific physiological signals or changing the infusion doses in emergency cases.

There is no need in clinical settings to divide anesthesia delivery systems into two non-collaborative, separated groups (i.e. open- and closed- loop). Even if most of the anesthesia control research revolves around self-adaptive and human-independent closed-loop systems, the human-machine collaboration is expected to bring added value for the maintenance of the set anesthesia depth. The solution can be the (semi-automated) hybrid systems, that allow the interaction of the anesthesiologist with the controller, which reacts on his actions (e.g., additive boluses), thus avoiding several complications (e.g., anesthesia awareness) [14]. Moreover, these systems provide support to anesthesiologists in clinical decision making process through the presentation of the decision inference. The latest was reliably made by processing the available contextual data and implying guidelines compliance.

Decision support systems (DDSs) have been developed for accurate detection and alert of peri-operative issues, using algorithms based on expert clinical knowledge or artificial intelligence patterns [15]. Characterized by context awareness, DSSs sense context information, evaluate the modeled processed data with different reasoning techniques and disseminate the context-related information to the general decision making element. Finally, the executive element can be a system component (e.g., infusion pumps in closed-loop systems) or the user (e.g., anesthesiologist in open-loop systems). An example of a DDS is the Smart Anesthesia Manager that implements a comprehensive set of decision conditional logic [15]. Moreover, the incorporation of smart alarm monitoring has been reported as part of a Hybrid Sedation System [16]. It rapidly integrates multiple signal sources and models in order to process the information received (i.e., the reactions to medications), finally generating a knowledge-driven decision based on similar reasoning to experienced anesthesiologists. In cases of emergency, the DDS are accompanied by alarms for low heart rate (HR), low respiratory rate (RR), low mean arterial pressure (MAP), and low peripheral oxygen saturation (SpO_2). A new decision support algorithm based on predictive state representation of anesthesia has been clinically tested, employing apprenticeship learning [17].

In both current clinical practice (open-loop) or automatic systems (closed-loop), the objective is the same: to achieve

the best possible outcome for the patient. In order to do this, it is necessary to reach and maintain the ideal clinical and therapeutic drug effect as accurately as possible for the desired time. The clinical common cycle is a quintessential example of feedback control, and therefore the combination of clinical and control engineering knowledge has been intensively researched to improve the drug-delivery processes.

The motivation of using automation in clinical anesthesia delivery is founded in patient safety, a key issue with implications from multiple matters:

- drug dosing regimen optimization – allows better personalized approach and knowledge-based precision therapy with higher reproductibility [9], [18];
- outperfomance of manual control – is assured through better stability of set points, demonstrating consistent application of best clinical practices [6], [19], [20];
- minimization of accidental over- or under-dosing – is obtained by avoidance of human distractions or bias introduced by possible burnout or emotional well-being of the practitioners [21];
- detection of critical events about patient's safety – promptly alerts clinicians for their intervention [16];
- decision support – provides anesthesiologists with the optimal drug infusion recommendation calculated from context-aware strategies;
- workload reduction and vigilance increase of clinicians – benefits from the release of the anesthesiologists from repetitive trivial tasks, allowing them to focus on decisions that require human cognitive processes, emergency clinical decisions or medical staff cooperation;
- cost-effectiveness – quantifies the performance of closed-loop standardized drug delivery in health organizations, described by the limitation of unnecessary treatments, cost-savings associated with goal-directed drug delivery; finally, this technology equals an expert provider and makes it an opportunity in underdeveloped regions with minimal resources.

III. CONTROL ENGINEERING ASPECTS FOR ANESTHESIA APPLICATION

A. INTEGRATED CLOSED-LOOP SYSTEM DESCRIPTION

A descriptive schematic of a closed-loop system is presented in Fig. 2, distributing anesthesia paradigm in computer-controlled and common manual optimization, as follows: multi-input multi-output integrated regulation (left side) and multiple drug dosing infusions while patient's response is monitored (right side). The anesthesiologist has also impact on the automatic system of drug delivery, being an active part in the loop by directly operating on the patient when needed.

A benchmark patient simulator has been developed by the DYSC research group from Ghent University. This simulator provides the reader with an overview of the embedded features and possible changes into the state of the patient as to closely mimic the clinical and physiological states. The research team has used the 15 years experience in the topic and literature reports to distill and provide in an understandable and accessible manner the complex interactions and dynamics taking place. Where available, clinical data has been curated and used in the simulator parameters. The two systems described are the depth of anesthesia regulation system and the hemodynamic stabilization system. The objective, by developing such a benchmark simulator, is to encourage the community to work in a systematic and fair-to-compare context towards developing computer based control of multi-drug regulatory problems in this application field. The novelty is the provision of the patient simulator as to date no such tools have been previously reported in literature. The originality of the approach is the inclusion of synergy effects, antagonist effects, patient variability, clinical value intervals, nociceptor stimulation disturbance, and co-simulation of anesthestic and hemodynamic states along with their complex interactions.

The parallelism between the manual clinical practice and the automatic control optimization can be integrated for aiming optimal drug delivery by accounting the following components:

- patient: the system with various complex dynamics;
- surgeon's actions, often similar per surgery type in terms of procedural practice, which can be modeled in the entire process (i.e., surgical stimulation profile added as disturbance on the system, i.e. patient);
- anesthesiologist's actions: the disturbances on the patient in the control loop;
- syringe pumps: the actuators for the controller's outputs, for every drug infused in the patient;
- collection of sensors, which deliver information upon the physiological dynamics of the patient body;
- prediction models: essential for computationally modelling of drug dynamics in the body and the concentration-effect relationship in each patient;
- multiple-input multiple-output (MIMO) strategy, that assumes all the usual drugs used in clinical practice for anesthesia-hemodynamic system and their effects on each individualized output lest connections can be missed;
- controller and optimizer: calculate and adapt the optimal drug dose for the current patient's state.

B. SPECIFIC ISSUES FROM CONTROL VIEWPOINT

Closed-loop control of anesthesia delivery can be defined as setpoint following, whereby the controller adapts the system's single or multiple inputs (manipulated variables) based on the feedback from single or multiple system's outputs (controlled variable). As in typical control systems, in anesthesia are also envisaged minimal overshoot (as each drug has a maximum effective dosage with clinical effect), rapid target reaching, long time target maintaining, stability through disturbances rejection (surgical stimulation), and robustness against uncertainties (intra- and inter-patient variability) and state constraints. Moreover, technical constraints represented by the time taken for calculation should be overseen for

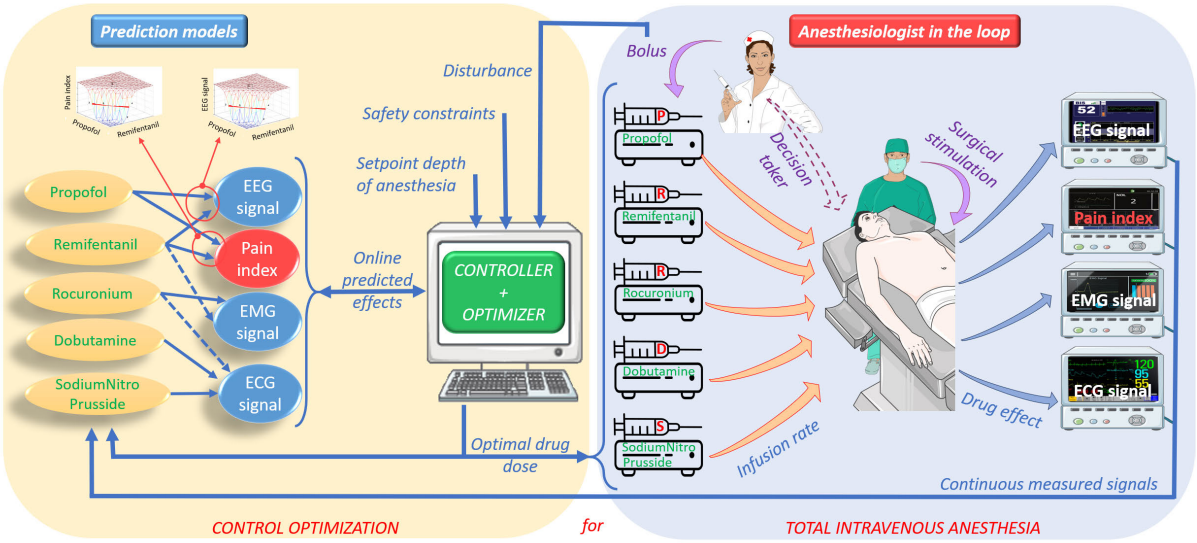

FIGURE 2. Closed-loop scheme for complete anesthesia paradigm automation in clinical practice.

anesthesia applied control where models adaptation and control optimization need to be done online in order to assure a real-time and minimum delay of drug infusion.

A control engineering viewpoint of the delivery anesthetics, in common with all other control problems, will include consideration of issues such as dynamic modelling, predictive and adaptive strategies, optimization algorithms, development of innovative monitors, coping with contextual uncertainty, and dealing with safety constraints. Since patient well-being is certainly of paramount concern, all the presented issues are equally relevant for engineers when designing the control scheme.

1) DYNAMIC MODELLING

The challenge for advancing closed-loop controlled devices relies on having sufficient understanding of patient pharmacological changes and copy them in model-based control strategies. An important issue is the credibility evidence supporting these models, so Parvinian *et al.* [22] examine the various uses of computational patient models in the design and evaluation of anesthetic delivery systems. The conclusion is that high variability characterizes the current evidence types that are already limited in scope and presentation.

The biggest uncertainty required to deal with is patient modelling, as physiological pharmacokinetics (PK) and pharmacodynamics (PD) of drug need to be accurately described through mathematics. Parameter uncertainty due to influence of surgical stimulation and other interventions or dynamics that remain un-modeled create hazards in control design. Present studies are performed in order to develop PK-PD models for anesthetics, including synergies between drugs and parameters identification, that can predict the patients' response [23], [24]. The introduction of covariates, available for a broad population, drives to uncertainty reduction.

Commonly, PK-PD compartmental models are used to predict the drug effect in time, combined with the nonlinear Hill curve relationship to the measured effect of drug [22]. Variations of the classical models have been studied for obtaining the most suitable model for control that still maintains the physiological accuracy. For example, an extension to fractional differential equations to account for tissue trapping has been proposed [25], considering that biological systems exhibit fractal kinetics (e.g., anomalous diffusion), while dismissing the assumption of PK models' homogeneity. During the last decade, the meaningful role of fractional calculus in modelling biological phenomena has emerged toward pharmacokinetics [26], [27].

Moreover, high fidelity PK-PD models are represented as transfer functions (input-output relationships) augmented by a delayed first order system model and the sigmoid linked to the measured effect (output) [28]. Another example is the work of Beck [29] that outlines the MIMO piecewise-linear and linear parameter varying PD models using BIS, testing them in a feedback control (gain-scheduling and adaptive methods). Based on another electroencephalographic (EEG) measure, named the Patient State Index, anesthetics were recently described on both population and individual levels [30]. While PD models have been developed for hypnotics to EEG-based signals and even synergistic drug interactions have been included, Hill curves that relate the concentration of opioids to their specific measured effect miss from clinical validation.

An alternative to classical PK-PD models are fuzzy models, that have the capacity to neglect some knowledge of the underlying physiology [31]. Using human heuristic logic, models that relate directly the infusion rate and BIS, avoiding the complexity of PK, have been proposed by Martin *et al.* [32]. Another advantage considered for fuzzy models over compartmental ones is the provision of an accurate

model based on universal approximator property, that can be used in predictive controllers to compute the optimal infusion [33]. In fluid therapy for maintaining the safety in hemodynamics variables, predictive models are used to accurately predict the response of a given patient to specific drugs [34].

The challenge for control standpoint represented by the nonlinearity of the Hill curve has been dealt with through a computationally efficient Hill curve adaptation strategy for BIS [35]. Furthermore, this new model formulation reduces significantly the numerical complexity of the online identification task in the process of model's adaptation. To overcome the drawback from the high number of PK-PD model parameters, but keeping the accuracy adequate for control, the parsimoniously parameterized model was the solution [36]. It does not have a PK-PD model, but it maintains a Wiener structure (third order state-space system) and a static nonlinearity. Pole placement choice on model identification has been simulated for control of opioids in order to achieve a good tracking performance compared with TCI [37].

Model adaptation or cost-function optimization are the key factors in dealing with inter- and intra-patient variability. Also, the individualized patient models permit the optimal delivery of drug dosing regimens once implemented in the controller design. This allows moving from conventional generic patient models for drug infusion regulatory loops to personalized medicine. Several strategies have been employed for adaptation of the dynamic part of the patient model, namely the PD parameters that need adaptation in function of patient's sensitivity to the drug [38]. The examples of PD parameters identification techniques include particle swarm optimization [39], extended Kalman filter [40], Bayes [41], nonlinear least squares [42], sequential quadratic programming [32], and genetic algorithm [33], [43]. The algorithms start from standard models and the values are continuously adjusted to reflect the time-variant patient's own parameters based on the individualized monitored response.

2) SENSORS FOR FEEDBACK

Closed loop control depends upon having a signal on which to provide feedback of the current state based on measured outputs. Such that, the anesthetic depth is monitored with multiple devices that complement the clinical examinations and conventional monitoring of vital signs. The concept of data acquisition is the fundamental capability of context-aware systems, characterized also by modelling, reasoning and dissemination of the decision in order to provide pervasive assistance to users (in open-loop systems) and machines (in closed-loop systems). Context-aware systems are already involved in many healthcare applications, especially in closed-loop control systems. Sensing context information is crucial in anesthesia regulation, considering context defined as the changing execution environment, where patient's states are of interest.

Each feedback depends upon unique concerns, such as the availability of measurements and the natural time constants associated with the variables of interest (e.g., delay in monitoring variables, time of patient's response to drugs etc.). The nature of the feedback problem varies from NMB to hypnosis or analgesia. Because of the well defined biomarkers, the effects of muscle relaxants on depth of NMB model are assessed by applying a train-of-four (TOF) stimulus of the adductor pollicis muscle, registered by electromyography (EMG) or other tools described in [36].

The hypnotic-related changes caused by different drug concentrations are tracked by EEG-based indices. For the monitoring of the brain's electrical activity, several processed EEG monitors have been developed, as follows: Bispectral Index (BIS), State and Response Entropy, Narcotrend Index, Patient State Index (PSI), SNAP II, Cerebral State Index, A-Line auditory evoked potential index, Wavelet-based Anesthetic Value for Central Nervous System index (WAV_{CNS}) [44]. The commonly used monitor uses BIS technology, the first clinically proven and commercially available direct measure of intraoperative hypnotic state. It is widely used as feedback in closed-loop control systems for regulating propofol or dual propofol-remifentanil, but other indexes have also been implied in automation (e.g., WAV_{CNS}). Based on the assumption that brain reactions to a strong nociceptive stimulus are not enough masked by anesthetic drug, BIS has been also used as the monitored variable for the synergistic drugs effect. However, one cannot consider EEG-based indexes for indicating the level of analgesia in the absence of a continuous nociception stimulus [45].

Development of novel sensors to provide a reliable and objective value of the nociception/ anti-nociception balance has been impacted closed-loop delivery of proper dosing. A comprehensive review on the commercial solutions that have appeared in recent years is done by Ledowski [46]. It tackles the monitoring limitations (e.g., non-specific markers, unknown robustness against the influence of other medications, influence of cofounding effects) of each device, deciding that the evidence to use one nociception monitor versus another is overall inconclusive. The same closure is defined in the recent systematic review of Meijer *et al.* [47] on 12 randomized controlled trials that used nociception devices for analgesia-guidance (i.e., Surgical Pletismographic Index, Analgesia Nociception Index, Nociception Level Index, Pupillary Pain Index (PPI), CARdiovascular DEpth of ANalgesia index). It concluded that no definitive agreement could be outlined about the effect of nociceptive monitoring on intraoperative opioid consumption, the results depending on each monitor. Another literature review by Gruenewald and Dempfle [48] regarding 7 randomized trials using different methods for analgesia monitoring and opioid peri-operative guidance reported a non-significant trend towards reduction of administered opioids and emergence time, mostly caused by the high heterogeneity of the trials included and by the non-focused clinical endpoints. Specifically, Nociception Level Index and Pupillometry had been observed in clinical trials to modify anesthesia care, resulting in less opioid use for nociception-guided

anesthesia using the nociception level monitor than the standard critical care [49], [50].

A systematic analysis is opportune for evidence of analgesia monitors' usability in computer drug delivery systems. Additionally, there are various research tools for the measurement of pain and nociception related to pathophysiological systems [51]. So, it is very important to consider the hypotheses being tested in the selection of the methodology for pain detection, in order to obtain the data of interest. Different variables and biomarkers can be considered for monitoring purposes or for the intended use in closed-loop control as feedback. Recently, a prototype device has been developed for intended use in closed-loop control of analgesia delivery, but only validation in post-anesthesia patients has been performed until now [52]. ANSPEC-PRO monitor, noninvasively measuring pain via skin impedance, allows identifying a mathematical model of the signaling pathways of nociceptor excitation [53].

In terms of control, there are still challenges around sensors for hypnosis and analgesia in TIVA, when they need to estimate online the fast changing environment and subsequently detect the clinically relevant differences (that sometimes may need good precision). Moreover, when one sensor is used as feedback in a closed-loop system that regulates only a specific input, but at the same time, the measured effect may be influenced by other inputs of the system, the effect of other drugs on the monitored variable are prior observed in open-loop set-up [54]. On the other hand, sensors are validated in typical surgeries that involve specific practices, different from the common routine (e.g., vascular surgeries, interventions in children), in order to test the ability of the device to adequately guide intraoperative drug administration during such uncertainties [55], [56]. A priori procedural methods or comparative studies are performed to better understand anesthesia end-points and to test the performance of anesthesia monitors under the same conditions [57]–[59].

C. AI: THE SOLUTION IN ANESTHESIA

In recent years, tools from artificial intelligence (AI) have been approached towards anesthesia monitoring. Large publicly available heterogeneous expert labeled data sets have provided several benefits for developing clinical decision tools using deep learning algorithms. One such application is EEG-based sleep scoring systems where the deep learning algorithm is trained to automatically score 5 sleep stages [60], [61]. Motivated by numerous studies demonstrating sleep-like inhibition of anesthetic drugs, and major breakthroughs in the application of deep learning algorithms for hypnosis monitoring and sleep staging using EEG, a novel data-repurposing framework to predict anesthesia-induced hypnotic levels from sleep EEG has been proposed. Deep learning algorithms learn patterns directly from the raw EEG data, eliminating the necessity to extract hand-crafted engineering features from EEG for prediction.

The use of deep learning tools to predict anesthetic drug-induced hypnotic levels based on sleep EEG data can be useful in developing hypnosis monitoring systems. Moreover, it has been indicated that deep learning techniques for hypnotic state demonstrated feasibility to validate and verify the robustness of clinical hypothesis using large-scale EEG data instead of visual assessments using traditional EEG spectrogram. It has been also shown that deep learning models generally allows reliable monitoring of hypnosis levels in new patients whose data were not included in the training process, thus the system can be used ''out of the box'' [62].

IV. CLOSED-LOOP CONTROL OF ANESTHESIA

Research into closed-loop anesthesia infusion systems has been increasing over the past decades, with a significant expansion during the last five years. This section overviews the control strategies tested in simulation or validated in clinical trials for anesthesia regulation in closed-loop. Database (ISI Web of Science) searches for *"closed-loop control of anesthesia"* yielded 428 articles. Refining the results for the time period 2015–2020, a number of 176 articles have been analyzed by years, authors, topic etc. The results are visually shown in Fig. 3. It can be noticed that the interest of both researchers and clinicians has increased with years. Also, it can be seen that Ghent University is the second top-leading institution with the authors of this article in top 10 leading authors with outstanding results in closed-loop control of anesthesia. In addition, the authors have also developed the first complete anesthesia-hemodynamic benchmark patients simulator. The aim is to encourage the community to work on in a systematic and fair-to-compare context towards developing computer based control of multi-drug regulatory problems.

Although the subtle advantages of closed-loop delivery to maintain a target BIS value may not be evident to practicing anesthesiologists, decreasing the percentage of time with BIS > 60 might help to reduce the risk of awareness. Moreover, reducing the workload of anesthesiologists with an automated system can have clinical significance by leaving anesthesiologists more time to control emergency hemodynamics, to manage the airway and ventilation, and to be even more attentive to the surgical procedure and the assessment of blood loss, etc. The remaining of this section focuses on the developed control strategies for general anesthesia with their advantages and limitations.

A recent review of an overall literature on physiological closed-loop control systems, including anesthesia, can be found in [31]. The considered control approaches in anesthesia are summarized as follows: proportional-integral-derivative control (PID), model predictive control (MPC), adaptive control (through online estimation and update of parameters integrated in models or control laws, or gain scheduling techniques), fuzzy-logic control and merged schemes, fractional order control (FO), internal model control (IMC), Bayesian control, back-stepping control, and positive control [44]. Furthermore, a narrative review is provided in [9], classifying the anesthesia autonomous systems in pharmacological (individualized drug titration),

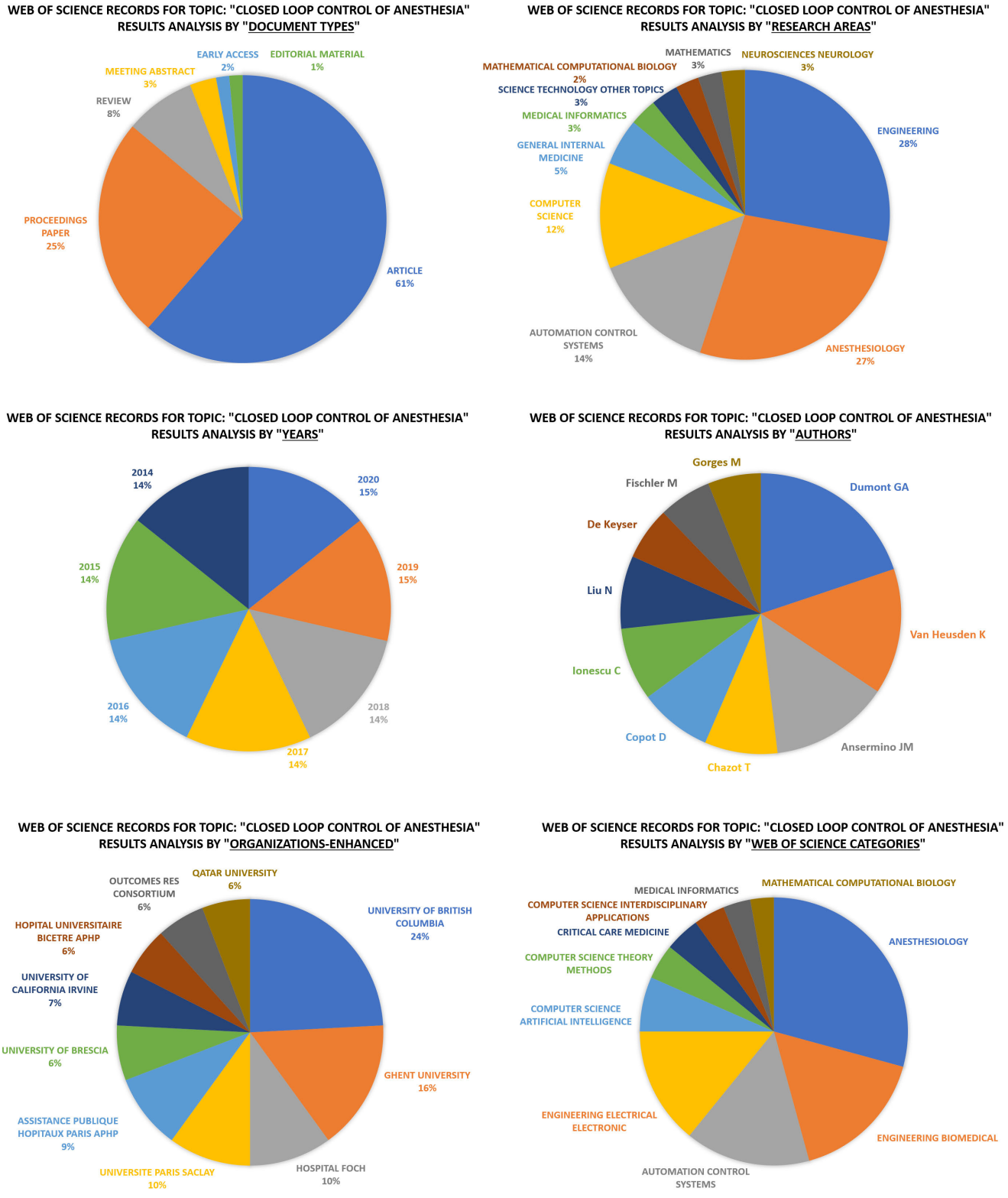

FIGURE 3. Web of Science records for "closed loop control of anesthesia" between 2014–2020.

mechanical (motorized tasks reproduction), and cognitive (decision support) robots. Because propofol is the most controlled drug employed in hypnosis regulation, the review in [63] compares different aspects of control algorithms using propofol infusion. Additionally, the outcomes of 36 and 12 randomized controlled trials comparing closed-loop

delivery systems versus manual control proved better performance for automation (i.e., better target following, decrease of over- and under-shooting, reduction of drug consumption during induction, and reduction of recovery time) [6], [19].

While anesthesia management assumes the integration of hemodynamics as a component of the complex peri-operative system, computer-controlled goal-directed hemodynamic therapy has found increasing interest [64]. In [65] the feasibility of centralized model predictive control (MPC) to the regulatory problem of hypnosis-hemodynamic variables has been investigated. This is novel in the application field and uses linear models which allow later on adaptive tuning to the patient characteristics, such as drug resistance, sensitivity, adverse effects, and drug retention times. The particular problem of drug trapping and non-homogeneous clearance rates has been addressed in [25].

The only closed-loop system that considers all the three components of anesthesia for regulation in a MIMO system is **McSleepy** (McGill University, Montreal, Canada) [66]. The completely automated closed-loop system using self-adaptive PID control has been successfully tested in cardiac surgeries. However, the infusion for maintaining NMB can be manually overridden, as the anesthesiologist is notified to confirm the bolus [67]. An important feature is the ability of the anesthesiologist to inform the device about different stages of surgery, in order to help its adaptation of drug infusion doses. The system incorporates safety features adapted for cardiac surgery requirements. Also a hybrid sedation system is introduced in [68] for closed-loop system for propofol sedation (single input) accompanied by a decision support system to detect respiratory and hemodynamic critical events (multiple outputs), validated in patients undergoing trans-catheter aortic valve replacement interventions [69]. Another safety system for closed-loop anesthesia supervision is proposed during propofol control conditioned by the monitored WAV_{CNS} [70]. The constrained PID based on viability kernel was implemented in **iControl** platform for clinical evaluation of control schemes. The extended safety system guarantees desired safety constraints, being validated also for reducing conservatism using model falsification [70]. Additionally, the work in [71] modified the control architecture with an explicit reference governor scheme for providing safety constraints satisfaction.

Analgoscore (or the modified version of it, namely NociMap), included in McSleepy, is the only monitored variable for analgesia reported in the latest clinical trials. Such that, [72] and [73] combine Analgoscore with PSI or BIS for feedback regarding the depth of hypnosis and analgesia in a fuzzy logic controller. Both controllers demonstrated their feasibility in clinical performance (i.e., maintenance of an adequate state of anesthetic depth up to almost 3 times compared to the TCI systems).

Attempting to control the entire anesthesia paradigm, a multiple single-input single-output (SISO) closed loop systems for each anesthesia component is used in [74], such as: dual PIDs for hypnosis and analgesia (through **Infusion Toolbox 95**), rule based adaptive PID for fluid therapy [34], [75], while ventilation is automated by the comercial device Zeus Infinity C700 Anesthesia (Drager Medical GmbH, Germany). However, their work does not integrate all anesthesia components into a single control strategy in order to assume the interactions between the inputs (i.e. drugs) and the outputs (i.e. monitored variables) of the system (i.e. the patient), even if no negative interactions between the 2 controllers have been observed. Studied in a randomized-controlled trial, the closed-loop system was superior to manual control and could influence postoperative outcomes. These systems use the MISO dual PID controller designed by [76] for maintaining the targeted BIS of propofol and remifentanil. Randomized clinical trials reported performance of the dual controller over manual control in terms of setpoint maintenance and postoperative outcomes [77], [78].

Several SISO and multiple-input single-output (MISO) systems for hypnosis control have been developed based on the common used BIS monitored variable as feedback. The control from [79] employs genetic algorithms for the offline tunning of event-based PID or model-based PID [80]. The work is continued in [81] through implementation of event-based predictive control extended with virtual actuator deadband. The latest demonstrated similar control accuracy with less control system effort compared to classical time-based predictive controllers. All the controllers are validated in simulation tests on patient models parameters extracted from clinical practice, plus generated by Monte Carlo method. For the control of both propofol and remifentanil co-administration as a MISO problem, [82] proposes a gain scheduled PID and particle swarm-based optimization technique. The same MISO design is validated in [41] for a Bayesian model-based adaptive control strategy using the software **RUGLOOP II** (Demed, Belgium). Additionally, the Bayesian model-based adaptive control is compared to manually adapted TCI and extended predicition self-adaptive control (EPSAC) during ICU sedation. Both computer-based control systems proved overall tighter control than human infusion, after robustness analysis using prediction error and spectographic analysis. Another MISO system linked to BIS for hypnosis and analgesia is the system designed in [83] that deals with online adaptation based on patients state observation [84] and positive control law.

The extensive research on the hypnosis regulation based on propofol to BIS relationship continues in the recent literature, confirming the need of improving performance even for this broadly proposed SISO system. The **CONCERT-CL** (Veryark Technology Co., China) closed-loop infusion system can automatically maintain the BIS value in an adequate range better than open-loop systems [85]. The system has been used for management of BIS by automated propofol infusion during a clinical trial aiming testing PPI for anti-nociception evaluation [86]. The work in [20] demonstrates the consistent performance of the common PID control in a multi-center trial using the patented **CLADS** (patent: 502/DEL/2003), compared with conventional manual control. The same

system is evaluated under the addition of dexmedetomidine that complements depth of anesthesia and reduces propofol usage without effecting awakening from anesthesia [87]. Besides, a conventional PID control is modified into an input-output inversion-based PI control in order to assure better robustness over inter- and intra-patient variability and noise [88]. Multiple other SISO adaptive control strategies for hypnosis include fractional order control [89], [90], ant colony optimization [39], multi-critic based neuro-fuzzy control [91], self-organizing fuzzy logic [92], [93], rule-based fuzzy logic [94], fuzzy predictive control based on genetic algorithm adaptive model [33], Smith predictor-based control scheme [95], feedback law with probabilistic certification (randomized optimization) [96], (offset-free) hybrid and model-based multi-parametric MPCs and state estimators [97]–[99].

The monitored variable WAV_{CNS} is used as target in the works of [100]–[102] for SISO control of hypnosis. Using multi-model based set of mixed controllers H_2/H_∞, in [100] it is achieved robustness to patient's drug response variability, output disturbance, and sensor noise, while attaining a good set point maintenance. In order to decrease the time of induction of anesthesia while maintaining robustness, [101] implements a manually tuned PID and a high-order Q-design controllers. Moreover, allometric scaling of PK-PD models reduces interpatient variability, allowing clinical evaluation of the robust PID control of anesthesia in children. On the other hand, habituating control is implied in [45] and [103] for a MISO system, using WAV_{CNS} for feedback in the control of hypnosis and analgesia.

The actions of the anesthesiologist are introduced in the robustness analysis in [14], where the bolus given by the expert is dealt with as disturbance. MPC-EPSAC strategy obtained robustness over inter-patient variability and 10 additional bolus injections in simulation [5], but also IMC has been reported with similar performance [14].

Going to multiple drugs regulated through BIS in MISO systems, a PI Smith predictor-based on a delay-free and delay-included model of the patient outperforms satisfactorily manual practice, while dealing with the BIS delay [104]. On the other hand, increasing complexity of the control system by adding specific measured output for each input in MIMO designs provides specific feedback of the patient's response to each drug. Such a system is analyzed in [105] in ICU patients, using BIS and EMG for hypnosis-analgesia non-overshooting control with integrator, based on closed-loop eigenvectors and extended Kalman filter. In [106] a physiologically-based MPC is simulated, while making feasible the online clinical implementation due to the short time required for the controller calculations. Rather than BIS, cardiac output and respiratory rate are used as feedback for a two-mode semi-adaptive switching control of inter-medication synergy between propofol and remifentanil [107]. This work has been extended for infusion of medications with transport delay for the application of regulating cardiac output with propofol [107]. Moreover, regulation of propofol infusion is proposed in [108] with a reinforcement learning-based control scheme using BIS and MAP as controlled variables for ICU sedation during general anesthesia.

The third component of anesthesia, NMB, is reported to be controlled in SISO closed-loops in [36] and [40], that compare optimal control problem solved based on Linear Quadrtic Regulator versus Semi-Definite Program, but also formulate adaptive controller using positive law. The controller involves the inverse Wiener model's static nonlinearity and a positive compartmental control law for the linearized system, while reducing the complexity. It has been validated in trials using **Galeno** supervisory automatic drug administration system. Furthermore, adaptive PID with time-varying gain based on parsimonious Wiener PK-PD model is proposed in [109], avoiding oscillations.

In Table 1, an overview of the latest results in closed-loop control of anesthesia is presented.

V. DISCUSSION

Control of anesthesia rises several challenges for both clinical and engineering specialists, that once solved would lead to the following perspectives:

- The engagement of human cognitive process into the system has a great potential to increase the intuitive-driven detection of the risky events; there is the need to develop technology enablers and strategies for placing the human in the loop (i.e., understand and model the human-contributed action; adapt the controller with the interaction between anesthesiologist and CPS entities).
- The offset of non-technological barriers (i.e., recognition and clinical adoption) constitutes a critical factor in success of socio-technical systems for medical decision support, poorly addressed by researchers, but essential.
- The complex procedure of general anesthesia can be computer-assisted in clinical practice; the high system complexity needs to be undertaken in terms of suitable modelling of MIMO interactions and stable control with feedback from multiple variables; robustness simulation should deal with the already studied intra-patient and inter-patient model variability and uncertainty, but also with the additional bolus in the loop and surgical stimulation (for disturbance rejection).
- The ability of a (model predictive) controller to anticipate future system's output could play an essential role in emergency; it demands accurate patient's model, or stability analysis that studies the unmodeled dynamics; model uncertainty and lack of persistent excitation in manipulated inputs to allow model identification are the two additional challenges from patient view-point. The uncertainty comes from the inter/intra-patient variability in response to drug amounts and effects, which requires either adaptive models or robust control strategies.
- Individualized patient's dose-response relationship estimation in real time will enable personalized treatment; adaptation strategy based on online identification of the

TABLE 1. Control techniques.

#	Author	Year	Controlled variable	Measured variable	Inputs/Outputs	Simulation/Trial	References
1	Penaranda et al.	2020	Hypnosis/Analgesia	PSI/Analgoscore	MIMO	Trial	[72]
2	Zixiao et al.	2020	Hypnosis	BIS	SISO	Simulation	[93]
3	Eskandari et al.	2020	Hypnosis/Analgesia	WAV	MISO	Simulation	[103]
4	Joosten et al.	2020	Hypnosis/Analgesia	BIS	SISO	Trial	[74]
5	Casas et al.	2019	Hypnosis/Analgesia	BIS/Analgoscore	MIMO	Trial	[73]
6	Regina et al.	2019	Hypnosis/Analgesia	BIS/EMG	MIMO	Simulation	[105]
7	Liang et al.	2019	Hypnosis	BIS	SISO	Simulation	[39]
8	Neckebroek et al.	2019	Hypnosis/Analgesia	BIS	MISO	Trial	[41]
9	Dutta et al.	2019	Hypnosis	BIS	SISO	Trial	[87]
10	Savoca et al.	2019	Hypnosis/Analgesia	BIS/MAP	MIMO	Simulation	[106]
11	Medvedev et al.	2019	NMB	NMB level	SISO	Trial	[109], [110]
12	Nogueira et al.	2019	Hypnosis/Analgesia	BIS	MISO	Trial	[83], [84]
13	Patel et al.	2019	Hypnosis	BIS	SISO	Simulation	[95]
14	Reboso et al.	2019	Hypnosis	BIS	MISO	Simulation	[104]
15	Khodaei et al.	2019	Hypnosis	BIS	SISO	Simulation	[91]
16	Merigo et al.	2019	Hypnosis/Analgesia	BIS	MISO	Simulation	[82]
17	Yousefi et al.	2019	Hypnosis	WAV	SISO	Simulation	[70]
18	Hosseinzadeh et al.	2019	Hypnosis	WAV	SISO	Simulation	[71]
19	Neckebroek et al.	2019	Hypnosis	BIS	SISO	Trial	[111]
20	van Heusden et al.	2019	Hypnosis	WAV	SISO	Trial	[28], [102]
21	Yu et al.	2018	Hypnosis	BIS	SISO	Simulation	[92]
22	Jin et al.	2018	Inter-medication synergy	CO/RR	MIMO	Simulation	[107]
23	Copot et al.	2018	Hypnosis	BIS	SISO	Simulation	[14]
24	Joosten et al.	2018	Hypnosis/Analgesia	BIS	MISO	Trial	[34], [75], [112]
25	Merigo et al.	2018	Hypnosis	BIS	SISO	Simulation	[80]
26	Navarro et al.	2018	Hypnosis	BIS	SISO	Simulation	[90]
27	Mendez et al.	2018	Hypnosis	BIS	SISO	Trial	[94]
28	Sadati et al.	2018	Hypnosis	WAV	SISO	Simulation	[100]
29	Cotoia et al.	2018	Hypnosis/Analgesia	BIS	MISO	Trial	[78], [113]
30	Alamir et al.	2018	Hypnosis	BIS	SISO	Simulation	[96]
31	van Heusden et al.	2018	Hypnosis	WAV	SISO	Trial	[28], [101]
32	Padula et al.	2017	Hypnosis	BIS	SISO	Simulation	[114]
33	Copot et al.	2017	Hypnosis	BIS	SISO	Simulation	[89]
34	Merigo et al.	2017	Hypnosis	BIS	SISO	Simulation	[79]
35	Pawlowski et al.	2017	Hypnosis	BIS	SISO	Simulation	[81]
36	Zaouter et al.	2017	Sedation	BIS/RR/SpO_2	SIMO	Trial	[68], [69]
37	Nascu et al.	2017	Hypnosis	BIS	SISO	Simulation	[97]
38	Nascu et al.	2017	Hypnosis	BIS	SISO	Simulation	[98]
39	Ingole et al.	2017	Hypnosis	BIS	SISO	Simulation	[99]
40	West et al.	2017	Hypnosis/Analgesia	WAV	MISO	Trial	[45], [115]
41	Padula et al.	2016	Hypnosis	BIS	SISO	Simulation	[88]
42	Mendez et al.	2016	Hypnosis	BIS	SISO	Trial	[33]
43	Zaouter et al.	2016	Hypnosis/Analgesia/NMB	BIS/Analgoscore	MIMO	Trial	[66], [116]
44	Ionescu et al.	2015	Hypnosis	BIS	SISO	Simulation	[38]
45	Orliaguet et al.	2015	Hypnosis/Analgesia	BIS	MISO	Trial	[77], [113]
46	Puri et al.	2015	Hypnosis	BIS	SISO	Trial	[20]
47	Regina et al.	2015	Hypnosis	BIS/MAP	MISO	Simulation	[108]
48	Liu et al.	2015	Hypnosis/Analgesia	BIS	MISO	Trial	[76]
49	Zabi et al.	2015	Hypnosis	BIS	SISO	Simulation	[117]
50	Ionescu et al.	2014	Hypnosis/Analgesia	BIS/EMG	MIMO	Simulation	[5]

PSI = Patient state index, BIS = Bispectral index, WAV = Wavelet-based Anesthetic Value, EMG = electromyogram, MAP = mean arterial pressure, NMB = neuromuscular blockade, CO = cardiac output, RR = respiratory rate, SPO_2 = oxygen saturation, MIMO = multiple-input multiple-output, SISO = single-input single-output, MISO = multiple-input single-output.

population models parameters is required to support and enhance the medical stuff operations in changing environments; compensation of the PD model nonlinearity and variable delays poses special challenges for control design and control stability.

- MIMO strategy is the closest to clinical practice, as multiple drug doses are optimally infused in the patient based on specific output measurement; opioid-analgesia balance requires a direct measure of the specific analgesic effect, so an analysis of the current available commercial nociception devices should be done.
- Teleanesthesia, when anesthesia is remotely controlled, could become possible whenever personnel with great qualifications is not available or need support, but also during robotic surgeries.
- In order to ease the introduction of automatic systems in routine use, the technology needs to be reliable and understandable for the medical experts; for the latest, user-friendly interface and transparent theoretical methodologies need to be provided together with safe boundaries working mode and smart alarms; on the other hand, when exploring the risk-benefit relationship, aspects should be considered in real clinical conditions.
- In order to increase the reliability of practitioners in automation, tests in clinical trials of the feasibility of the closed-loop controller are necessary as proof of concept; later, larger clinical studies are needed in a multi-center design to provide evidence based on reproductibility of the results and comparison to a control group (i.e. manual infusion); this is necessary to overcome the opinions that the simulations of new controllers meet the well-known engineering principles for the validation of the innovative control strategy, but the clinical significance lacks to be demonstrated.
- The navigation of the regulatory landscape for medical devices that incorporate advanced levels of automation is an important issue that needs to be taken in consideration by the stakeholders, from the viewpoints of design, implementation, and evaluation considerations.

VI. CONCLUSION

Anesthesia titration in a closed-loop controlled manner remains a research tool that is not yet implemented in clinical care. Although the advance in research on both physiology and technology has enabled automation of the complex anesthesia process, the actual control strategies are far from the mature state needed to be integrated in standard hospital use. The issue can be explained by the limitation of the current control systems to not copy the real-life clinical routine of the complex anesthesia by means of integrated regulation of all anesthesia-related drugs (for hypnosis, analgesia, neuromuscular blockade, hemodynamics, respiratory dynamics). However, this is just a question of time, as several in-silico simulations but also clinical trials have demonstrated the benefits of anesthesia regulation in terms of patient safety, experts support, and economical impact.

The breakthrough in this area will be the development of medical cyber physical-human systems that integrate context-awareness, devices communication, human-machine cooperation, control and optimization algorithms for accurately making the right decision for drugs infusion.

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