Towards Automation in Anaesthesia

A review

Catarina S Nunes
Department of Sciences and Technology (DCeT)
Universidade Aberta
Lisboa, Portugal
CatarinaS.Nunes@uab.pt

***Abstract*— Surgeries represent a risk for patients and a big cost for the hospital. Anaesthesia represents a complex part of surgery also carries risks for patients. The most known are awareness (with deep psychological consequences); increased risk of morbidity and mortality; adverse reactions and long post-op recovery. The complexity of anaesthesia management can be reduced by studying the patients' responses and developing indicators of the patient state. To assess the level of depth of anaesthesia, the anaesthetist needs to be aware of the patient physiological responses to the drugs and to surgical stimuli. A system that could advise on the patient state considering all clinical signs being measured, the patient individual response and the amount of drugs, will have a big impact on patient overall safety and future health, post-op recovery and hospital resources. This paper does a review of different systems and methods applied to several aspects of the anaesthesia field. All with the goal of working towards automation in this very complex area, that involves high risks for patients. This paper covers advisor systems; signal processing; new monitors and devices; mathematical modelling; and control algorithms; all focused on practical clinical implementation. The objective is to have an overview of the work done so far and the steps taken towards automation in anaesthesia.**

Keywords— anaesthesia; automation; signal processing; control; modelling; medical devices

I. INTRODUCTION

Anaesthesia comprises muscle relaxation, analgesia and unconsciousness, i.e. depth of anaesthesia can be defined as the lack of response and recall to noxious stimuli. Throughout a clinical procedure, anaesthesia must be titrated. Insufficient anaesthesia results in awareness (100-200 cases per day in USA [1]), at its worst consciousness and pain in a paralysed patient, cardiac problems (ischemia, infarction). Excessive anaesthesia is associated with increased morbidity and mortality at 1-2 years post-op [2].

Anaesthetists use a variety of observations, as blood pressure, heart rate, movement, sweating, pupil response, EEG (electroencephalogram) indexes, to make a judgement on anaesthesia level [3]. The introduction of balanced anaesthesia (the use of three drugs: muscle relaxant, analgesic, anaesthetic) improved the patient safety, but the clinical signs are obscured by the effect of the different drugs and its interactions. Drugs may increase/decrease the effect of each drug, potentiate the side effects or introduce new side effects [4]. The clinician needs to be aware of drug interactions for the safety of the patient. At large, the anaesthetic drug is combined with one of the synthetic opioids to provide analgesia. But, the optimal infusion rate/concentration is largely affected by the choice of opioid. Also EMG activity interferes with the EEG processing making the assessment of unconsciousness even more difficult.

The development of pharmacokinetic and dynamic (PK/PD) population models for anaesthetic drugs and its integration in target controlled infusion (TCI) pumps was an improvement in helping the clinician to target drug concentrations. But, these models do not adjust to the patient individual responses or changes in haemodynamics.

The complexity of anaesthesia management can be reduced by studying the patients' responses and developing indicators of the patient state. To assess the level of depth of anaesthesia, the anaesthetist needs to be aware of the patient physiological responses to the drugs and to surgical stimuli. Although different anaesthesia monitors (heamodynamic, EEG, etc.) are used, the information is not combined, analysed or crossed checked. A system that could advise on the patient state considering all clinical signs being measured, the patient individual response and the amount of drugs, will have a big impact on patient overall safety and future health, post-op recovery and hospital resources.

The complexity of the human body and the specificity of anaesthesia with all its risks is an area of health sciences where advisor systems can play a key role in improving healthcare by reducing adverse events, recovery times, hospital stay and occurrence of re-interventions. A big challenge is also to determine the patient's perception of pain under anaesthesia, there is no objective indicator that could be used to determine the adequacy of the level of the analgesic drug and the patient response to painful stimuli.

This paper does a review of different systems and methods applied to several aspects of the anaesthesia field. All with the goal of working towards automation in this very complex area, that involves high risks for patients.

First, advisor systems will be presented, many from industry. Secondly, the different signal processing research

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work that has evolved in the search for a reliable anaesthesia index. Thirdly, the development of new monitors and devices that help to access the patients' response to the drugs and also to surgery (e.g. surgical stimulus). Then a more extensive review of different research groups that focus on mathematical modelling of the anaesthetic drug effects', and on different control approach being it on simulation only or already with results in practical clinical implementation.

II. Advisor systems

There are some advisor software developed by industry with different approaches for the anaesthesia area.

GE Healthcare has the Navigator [5] and Dräger the SmartPilot View [6], which are similar software that using PK/PD population models show estimated drug concentrations for any given dosage, taking into account known interactions and probability (e.g. 50% of people will not respond to incision with this amount of drug). These software are very useful in places such as the USA were TCI pumps are not available. But, none of these software takes into account the patient physiological responses to the procedure, interact with the clinician, analyse the patient stability or react to alarms.

Other software shown as advisor/intelligent anaesthesia systems, relate to resources management, patient data recording or scheduling, such as the Philips' IntelliSpace [7], Picis' InSight Anesthesia [8] or the McKesson Anesthesia Care™ [9]. There is a publication from the University of Washington [10] that presents a Smart Anesthesia Manager, which is tested for the timely use of antibiotic and other drugs, and for the billing management of such events.

The University of British Columbia has the iKnow [11] software that allows a clinician to build he/she own set of rules, and is working towards a navigation software, although details are not known.

III. Monitors and Anaesthesia devices

During the last decades the medical industry has invested in new monitors based on different approaches of analysis of the EEG signal. The most recent is the qCON developed by Quantium Medical, qCON is a level of consciousness index based on proprietary technology of the company [12]. They also have a monitor called qCON-NOX which is a novel technology. The qCON index defines the hypnotic effect and the qNOX index defines the pain/nociception. They are both derived from the EEG, a direct measurement of brain activity and from the same recording a measure of hypnotic effect and a measure of pain/nociception is obtained. This technology is still very new and recently presented in the 2013 Annual American Society of Anesthesiologists Meeting (the biggest conference of the anaesthesiology area, more than 17,000 participants), it is still lacking publication studies and it reliability compared to the widely used monitors is still not tested.

The most used monitor based on the EEG, with thousands of publications and millions of patients analysed is the BIS™ Monitor from Covidien [13]. The BIS monitor is currently used all over the world, it has been extensively validated and many research work has proven its utility and safety to detect awareness during anaesthesia. The bispectral index (BIS) of the electroencephalogram (EEG) is a numerical processed, clinically-validated EEG parameter, used as an indicator of the level of hypnosis. The BIS is a number between 0 and 100, where values near 100 represent an "awake" clinical state while 0 denotes the maximal EEG effect possible (i.e., an isoelectric EEG). During surgery, the level of hypnosis should be driven to a value between 40-60 and maintained there [14]. The Cochrane Review on BIS monitoring showed a significant reduction in the cases of awareness when anaesthesia is guided by the BIS monitor [14]. This was one of the major publications impersonating the use of brain monitoring during anaesthesia to access the patient level of unconsciousness. The major national anaesthesia society's advice the use of brain monitoring [15].

A recent review was done on the effectiveness of different general anaesthesia brain monitors [16]. The objective of this report was to assess the clinical effectiveness and cost-effectiveness of BIS, E-Entropy and Narcotrend technologies, each compared with standard clinical monitoring, to monitor the depth of anaesthesia in surgical patients. They reported that the analysis was limited by lack of clinical effectiveness data, particularly for E-Entropy and Narcotrend [16]. But, there were reductions in general anaesthetic consumption and anaesthetic recovery times, which has by itself a considerable impact in patient welfare.

The Entropy monitor from GE Healthcare is the second most widely used depth of anaesthesia monitor [17]. It has been validated and used extensively, it is based on the EEG activity of the frontal cortex (same as the BIS index) but the signal processing techniques to extract and compute the index are different. There is always an open debated on the differences between the several monitors/indexes and its effectiveness in detecting different states of anaesthesia.

One of the problems reported with several monitors is the time delay. The work in [18] reports not constant time delays which ranged from 18 to 152 seconds. These time delays were different for increasing and decreasing index values, and dependent on starting and target index values. The major conclusion is that time delays of index calculation may limit the monitor's ability to prevent awareness.

The SEDLine monitor from Masimo is a more recent monitor that BIS, and uses a sophisticated multivariate algorithm to assess EEG data from all 4 channels and determine the Patient State Index (PSI™) value as a measure of anaesthetic depth [19]. The innovation of SEDLine and the PSI is the use of the 4 channels of the EEG. The SEDLine monitors bilateral brain function and symmetry with a density spectral array display [20]. This is a major advantage for research purposes but also for experiences anaesthesiologists that can analyse the complex EEG information, in this way it improves the possibility of detection of adverse events.

The revolutionary monitoring system in 2013 was the SEDASYS® Computer-Assisted Personalized Sedation System [21]. The system was presented in the 2013 Annual American Society of Anesthesiologists Meeting and approved by the FDA. The SEDASYS® System is the first Computer-Assisted Personalized Sedation system. It is designed administer minimal-to-moderate propofol sedation by integrating patient monitoring and drug delivery. The system is design to be used in colonoscopy and esophagogastroduodenoscopy procedures only with healthy adult patients, and can also be used by non anaesthesiologists. It is a very rule base and alarm lead system, with little risk of over sedation, with patient feedback (response to commands). It is not designed or approved to be used under general anesthesia since it needs the patient response to auditory commands. Nevertheless, it is a very important step towards automation in the area.

To finalize this section a note on a new concept of anaesthesia monitoring. The LiDCO*rapid*^{v2} is the first multiparameter hemodynamic monitor, which can integrate an optional module (BIS^{TM}) for EEG signals, providing the extra ability to monitor the state of the brain [22]. The LiDCO noninvasive monitor was designed to do real time processing of blood pressures, heart rate, stroke volume and cardiac output, pulse pressure variation and stroke volume variation. The new version can also incorporate brain monitoring (BIS), this is a step towards incorporating the research which proves that changes in patient's hemodynamics changes the drugs PK-PD, and with that the drug effects (level of anaesthesia).

IV. Signal Processing

Behind the development of the different monitors is a long research work on the application of signal processing techniques to EEG and other signals, such as Evoked Potentials. The work in [23], a review of the principles underlying processed electroencephalogram (EEG) monitors is done. This research shows that current processed EEG monitors are limited by their calibration range and the interpatient variability in their dose-response curves. Therefore it is still necessary to understand the transformations of cortical and subcortical activity into EEG signals, the effects of anaesthetics at a systems level, and the neural correlates of consciousness [23]. There still work to be done in the signal processing area.

In work [24], new advances in the processing on EEG and Auditory Evoked Potentials (AEP) are presented. The AEP have been widely studies for the evaluation of depth of anaesthesia. In fact they were one of the first signals to be correlated with anaesthetic depth and one of the first to be used for modelling and control [25, 26]. The three wave AEP pattern, is associated with a depth of anaesthesia at which awareness occurs.

Different signal processing techniques have been used to extract the relevant features from the AEP signals and to compare the result with clinical gold standard evaluation. The discrete time wavelet transformation can be used for compacting the AEP and localize the time and the frequency of the waveform [27]. In this work, step discriminant analysis is used to selected those wavelet coefficients which best distinguish the waveforms of those responders from the nonresponders, this are then used to train a four-layer artificial neural network for classifying between the responders and the nonresponders. While in [28], model-based algorithm based upon autoregressive with exogenous input (ARX) models is used to improve the signal-to-noise ratio and qualitative fuzzy logic to create a reliable index for monitoring depth of anaesthesia. In contrast, [29] uses signal do noise reduction techniques based on simulations and the underlying characteristics of the AEP.

[30] is the most recent work with AEP processing, It shows multi-resolution wavelet analysis as a feature extraction method from recorded AEPs during anaesthesia. The combination of these features with a fuzzy logic rule-based inference has been shown to successfully predict the underlying DOA remarkably well.

The signal processing techniques applied to EEG, are frequency based and have a wide range of techniques: bispectral analysis (such as the BIS); entropy; fuzzy logic (such as the cerebral state index - CSI [31]); symbolic dynamics (such as the IoC [32] from Morpheus Medical). The IoC monitor uses the combination of spectral ratios, symbolic dynamics EEG and suppression rate for analyzing the EEG [32]. The underlying algorithms for most of the EEG based monitors proprietary and therefore only the generalities are known. Exception for the entropy monitor of GE Healthcare [17], where the Shannon Entropy algorithm is published.

V. Mathematical Modelling

Many of the research being dine is also with the goal to model/predict drug effect, and patient's response to different drug combinations (being in different doses or also type of drugs). Drug interactions are of major concern, since the analgesic and anaesthetic drugs are interconnected, because they interact with each other so as to achieve an adequate level of depth of anaesthesia and analgesia [33]. This interaction is often synergistic, meaning the drugs potential the effect of each other, this is of major concern since they can also potentiate the side-effects. Another factor is that this interaction is different according to the different drugs. The work in [34], shows the different interaction curves and 3D modelling for different drug combinations.

In [35], a fuzzy logic patient model was developed that integrates the interaction between analgesic and anaesthetic drugs but also surgical stimulus on the haemodynamic and AEP responses of the patient. A neuro-fuzzy logic was used in [36] but using the BIS as the measure of effect and real clinical data.

Another important work is the one in [37], which build the basics for surface models for the drug interaction effect on brain signals, being it a synergistic or additive interaction. This models are also called the multivariable Hill equation models. The univariate Hill equation (or Emax model), is the most used PD model structure for intravenous drugs.

Our previous work also had this goal in mind, trying to identify different patient characteristics and the effect on the drug requirements, studying modelling strategies for patient response prediction [38]. Two studies also show that the choice of PK model influences the adequacy of the model and that the patient haemodynamics have a big influence in drug metabolism [39, 40].

VI. Control Systems

There are groups that have been working with automatic control systems for the administration of the anaesthetic propofol, this is a challenging area. In these papers, different EEG indexes are used to guide the infusion dose of propofol according to a reference value. Different control algorithms are applied and its performance tested in clinical practice. These closed-loop controllers are a good help for the anaesthetist, since they titrate the drug infusion rate in a fast way. But, they do not incorporate other physiological patient variables or navigate towards an overall stable state. And many are still in simulation only.

One of the first studies ever published was [26], using AEP in dogs and the anaesthetic controller used a 4-layer artificial neural combined with fuzzy logic and rule-based control. Acceptable clinical performance was obtained in 10 dogs, showing the feasibility of this approach. However, it never reached human clinical trials.

In the research done in [41], a proportional integral (PI) controller was used to determine the target blood concentration of propofol required to induce and maintain general anaesthesia automatically using AEP as the measure of effect. This work was done in 100 spontaneously breathing patients, and there were no reported cases of awareness.

The AEP were also used by [42], as a measure of effect when building a multivariable fuzzy logic controller for the co-administration of intravenous anesthetic and analgesic drugs. The work was done in simulation only, but proved to be robust and easy understandable by the clinician.

[43] developed a very interesting approach using a Bayesian-based closed-loop control system for propofol administration using the BIS as a controlled variable. This controller performed accurate during anesthesia for ambulatory gynecological procedures, meaning small procedures, and showed potential for clinical trials.

Another approach to closed-loop control in the anaesthesia area is the Rostock assistant system for anaesthesia control (RAN) [44]. This system the multiple-input–multiple-output control of hypnosis and neuromuscular block has been shown to be possible as well as the closed-loop control of a deep arterial hypotension, this system is being tested in patients and seems to be showing promising results (according to the authors).

The model based EPSAC (Extended Prediction Self-Adaptive Control) scheme for control of depth of anaesthesia, is also being developed [45]. And has showed promising results in simulation (clinical trials undergoing), and also in intensive care units. The idea of switching and adapting the control strategies showed a good performance during the induction phase in simulation studies [45].

The idea of adaptive control systems for such a complex problem as general anaesthesia under surgery, is a great challenge but also a step towards individualized patient care, and a way to deal with the high inter and intra patient variability. [46] presents an extensive simulation study in individually adjusted patient models (so cover the population variability) of an adaptive control structure. The results show a good potential, and the MUSMAR control structure can handle well disturbances and high uncertainty.

A research group that has presented strong work on the area of control in anaesthesia is [47, 48]. Their work show a systematic procedure to design both robust PID controllers and robust controllers based on fractional calculus, to regulate the hypnotic state of anesthesia with the intravenous administration of propofol. They also focus on optimization of anesthetic drug administration, the problems that arise and also the performance measures that are (often) not adjusted to the particular case at hand.

The work in [49] described all the work done so far in the University Hospital in Bern, and ZTH, to develop, test and validate multitasked closed-loop control systems for different end-point in anaesthesia practice. Overall 150 patients were treated using closed-loop controller under general anaesthesia. Different variables are analysed for control purposes: O_2, CO_2, and inspired and expired anaesthetic gas concentrations in the breathing system, as well as mean arterial pressure and depth of hypnosis through BIS. This work shows how control algorithms can be used in different approaches to guarantee a stability in different signals. The difficulty is in integrating this small systems into one, and also on how can such a control structure can be effectively used in clinical practice.

There have been some publications by another group [50], which has an impressive number of patients anaesthetized using a closed-loop systems for the intravenous drug propofol and the analgesic remifentanil. A closed-loop titration of propofol target control infusion based on a proportional-differential algorithm guided by the BIS, is presented in this work [50]. The authors show that automatic control of consciousness using the BIS is clinically feasible and outperforms manual control, in their patients.

The last study presented in this paper is the one in [51, 52]. In this work, a rule-based adaptive closed-loop system for intravenous anaesthetic drug propofol administration using the BIS is presented, the system's performance is compared with

manual administration. The controlled presented is a PID controller, single variable and is the system is called self-adaptive (by the authors) because it used the error of BIS and is an increment to the previous dose. In technical engineering terms, this is basically a PID controller. Never the less, it seems to have a better clinical and control system performance than manual administration (in 40 patients).

VII. Conclusion

Decision support systems help to make reliable and standardized decisions in complex environments, being clinical, industrial or environmental. Target-controlled infusion systems (TCI), although based on estimation and theoretical model, reduce the anesthetic workload. Closed-loop systems will automate anesthesia care in the near future [52]. Paper [53] presents an interesting perspective from a clinical point of view of automated systems in anaesthesia. It suggests that the future anesthesiologist may devote less time to easily delegated tasks when in the operating room, using the ability of computers to maintain variables in a set range allows some tasks to be automated.

Overall, the research on different steps towards automation in anaesthesia has been long and hard. But, the help that engineering gives to medicine is unquestionable. In the specific field of anaesthesia, there are still a lot to do so that one can cope with the high interpatient variability. When working with patients, the system under study is always changing, therefore all new devices, advisor, control and prediction algorithms, that can help access the patient state and reduce the occurrence of adverse effects, are in the end saving lives.

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