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Closed-Loop Control of Anesthesia - A Review

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Abstract: In many fields of human endeavour, ranging from the mundane such as DVD players to the technologically advanced such as space flight, control systems have become ubiquitous, to the point that control technology has been termed by Karl Aström the "hidden technology". However, in the field of anesthesia, despite efforts going back to 1950, closed-loop control is rarely used to automate the delivery of drugs to safely achieve and maintain a desired clinical effect. This might be because of the complexity of physiological systems, the poor understanding of anesthetic drug mechanisms, the large inter-patient variability, and the difficulty in sensing. Following a brief introduction to general anesthesia, those challenges will be reviewed from a control engineering perspective. Recent developments in sensing and monitoring have resulted in renewed interest in automatic control of anesthesia. These developments will be discussed, and then recent research in control of depth of anesthesia, as well as in analgesia, neuromuscular blockade will be reviewed. The appropriateness of various control methodologies for this problem will also be discussed.

Keywords: Anesthesia; Analgesia; Automatic drug delivery; Biomedical control systems; Closed-loop control; Medical systems; Physiological models.

1. INTRODUCTION

In anesthesia, the rapid onset of anesthetic drugs, as well as the required continuous monitoring of their dangerous side-effects, contrast with all other medical drug therapy. Theoretically, a tailored general anesthetic could be delivered through the use of a closed- loop controller without the need for expensive and time-consuming genetic prescreening. Anesthesia drug delivery involves the continuous administration of a combination of drugs with frequent adjustments to maintain normal cardiorespiratory vital signs during surgical stimulation. Recent advances in nervous system monitoring technology, however, have yielded a new set of real time sensors to capture the effect of these drugs on the patients state. As a result, automated feedback control of anesthetic drug delivery to a pre-defined setpoint can be a means to provide the patient with a titration specifically adjusted to his or her needs. This idea of automated anesthetic drug delivery has been investigated for over 50 years, however, despite rapid progress over the last ten years, no real clinical breakthrough has yet been achieved.

2. OVERVIEW OF ANESTHESIA

The goals of anesthesia are to allow the surgeon to operate in optimal conditions while protecting the patient from the effects of the surgical procedure and maintaining homeostasis and hemodynamic stability as much as it is possible. For this, the anesthesiologist administers a number of drugs to the patients: hypnotics that act primarily on the brain to induce unconsciousness (also known as hypnotic state) in the patient so as to prevent intro-operative awareness and memorization; analgesics to suppress nociceptive reactions in presence of painful stimulus; and sometimes neuromuscular blocking agents to induce paralysis in order to suppress reflex muscle activity. The role of the anesthesiologist is to carefully dose the amounts to avoid underdosing which can lead to intra-operative memorization and possible postoperative post-traumatic stress, as well as overdosing which, due to the toxicity of the drugs involved may lead to serious or even fatal intra or post-operative consequences for the patient.

There are two broad classes of anesthetic agents: inhaled agents and intravenous agents. Common inhaled anesthetics, often used in combination with nitrous oxide, are: desflurane, isoflurane and sevoflurane. Inhaled anesthetics have a combined hypnotic and analgesic effect but have also a strong hypotensive action. An advantage of inhaled anesthetics is that by measuring the difference between inhaled and exhaled concentrations allows an accurate estimation of plasma or brain drug uptake. Modern total intravenous anesthesia (TIVA) usually involves propofol as hypnotic agent and remifentanil as analgesic agent. Propofol is characterized by fast redistribution and metabolism, and provides rapid emergence and has good anti-emetic properties. Remifentanil is characterized by a very rapid onset and brevity of action, thus minimizing undesirable opioid-induced side-effects. That, combined with the high specificity of both agents, makes them them ideal for control of anesthesia. Hence, the vast majority of studies of closed-loop control of anesthesia have been

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performed using intravenous anesthesia. Finally, for neuromuscular blockade (NMB), agents such as rocuronium and atracurium are commonly used as a bolus as the beginning of the intervention to facilitate intubation, sometimes repeated during the intervention to provide optimal conditions for the surgeon if necessary.

We can divide the anesthesia procedure into 3 distinct stages: induction, maintenance, and emergence.

Induction. Induction, or the the phase during which the patient is being put to sleep , although quite short is critical in many ways. As soon as the patient loses consciousness, e.g. after a bolus of propofol, they will usually stop breathing and need to be rapidly intubated to allow artificial ventilation. To facilitate insertion of the endotracheal tube, the bolus of proposal is usually preceded by a bolus of opioid such as remifentanil. Furthermore, as soon as the patient loses consciousness, to blunt any reflex during intubation, a NMB is generally administered. In addition, overdosing of the patient at induction may lead to severe hypotension which will need to be corrected with vasopressors, and may place elderly or fragile patients into too deep an hypnotic state which may lead to prolonged periods of electrocortical silence, thought to have harmful long-term effects. Minimizing the amount of overshoot at induction is thus critical.

Maintenance. During that phase, it is necessary to maintain an adequate depth of hypnosis (DOH) and to blunt nociceptive reactions. When using inhaled anesthetics, the measurement of the end-tidal vapour concentration provides the anesthesiologist with a reliable feedback quantity. The situation is more complex with TIVA, as no arterial concentration of propofol or remifentanil is available. In the absence of brain monitoring, the anesthesiologist will use hemodynamic parameters such as heart rate and blood pressure for guidance, or watch out for patient movement. The development of TIVA has been made easier through the development of pharmacokinetic model-driven infusion devices. These devices reach a desired plasma (or effect site) theoretical concentration by using a computer-controlled infusion pump driven by the pharmacokinetic parameters of the drug. The resulting Target Controlled Infusion (TCI) (Absalom and Struys (2007)) anesthesia is used extensively in most of the developed world except in the USA where it is not FDA approved.

Emergence. The emergence from anesthesia is simply achieved by turning off delivery of the hypnotic and analgesic agents used during the surgery. This is usually done during skin closure so that the patient wakens up faster at the end of the surgery. An additional bolus of a long acting opioid may be given for postoperative pain management. Extubation takes place as soon as the patient shows clinical signs of wakefulness.

3. SENSING FOR ANESTHESIA

In this section, we will focus on sensing for the three major components of anesthesia, hypnosis, nociception and muscular relaxation. This is of course above and beyond the monitoring of standard physiological parameters such as heart rate, respiratory rate, minute ventilation, airway pressure, end-tidal CO_2 through capnography, blood pressure (either non-invasive or through an arterial line), oxygen saturation though pulse oximetry,

3.1 Sensing for Hypnosis

The effects of anesthetic drugs on the electroencephalogram (EEG) have been known since the early 1940's when neurophysiologists observed that the EEG of anesthetized patients contained slower waves with higher amplitudes. However, raw EEG are difficult to detect and interpret in real-time and thus a number of techniques have been used to extract univariate features from the EEG to quantify the hypnotic component of anesthesia. Two such features of historical interest are the Median Frequency (MEF) and the Spectral Edge Frequency (SEF), i.e. the frequency up to which 95% of the EEG power is present. However, this is not until the advent of the BIS^{TM}monitor that EEG has become more common place. The BIS monitor is based on the observation that with increasing anesthetic depth, EEG frequencies tend to synchronize. This lead to the use of the bispectrum to characterize phase coupling of different frequencies. The BIS^{TM}monitor combines a number of bispectra, bicoherence indices and power spectral values to derive a [0-100] index known as depth of hypnosis. An index of 100 represents the awake state while it decreases with increasing concentration of anesthetics. General anesthesia is obtained for an index between 60 and 40. Lower values represent deep hypnotic states, and usually are not desirable. Introduced in the mid-1990's, the BIS monitor largely dominates the market for DOH monitors.

The second most common DOH monitor is the M-Entropy^{TM}monitor, introduced in 2003, which provides two indices, the State Entropy (SE), a measure of the irregularity of frontal electroencephalogram activity within the frequency range of $0.8 - 32$ Hz; and the Response Entropy (RE), a measure of the irregularity of frontal electroencephalogram activity within the frequency range of $0.8 - 47$ Hz. While SE is a surrogate of the BIS, the difference between RE and SE is thought of as an indication of nociception because it may contain some facial electromyographic (EMG) component.

Although it provides anesthesiologists with a reliable index of hypnosis, the BIS introduces a large and variable delay, is inherently nonlinear, tending to evolve in stepwise manners during transient phases of anesthesia and is essentially a blackbox hard to characterize for control design purposes. On the other hand, the M-Entropy responds much faster, is a simpler algorithm but tends to provide a very noisy index.

The more recent NeuroSense^{TM}monitor that addresses those concerns was developed specifically for use in closed-loop control of anesthesia. It derives a bilateral index based on wavelet decomposition of a frontal EEG, with emphasis on the γ-band activity, (Zikov et al. (2006)). It has been shown to relate well with the BIS in steady state, but possesses much faster, delay-free and constant dynamics over its entire range, (Bibian et al. (2011)).

3.2 Sensing for Nociception

Sensing for nociception or analgesia has proved to be much more difficult to develop. In the absence of specific monitors, anesthesiologists assess the patient's nociceptive reactions by keeping a close eye on heart rate and blood pressure, both of which tend to increase sharply in case of a sympathetic response to a non-properly blunted noxious stimulus. To date, the only commercially available system is GE's Surgical Stress Index (SSI$^{\text{TM}}$) computed from finger photoplethysmographic waveform amplitudes and pulse-to-pulse intervals. The ANI$^{\text{TM}}$algorithm analyzes the tachogram with wavelets, and tracks the time-varying power in the HF band. It has been shown to respond to the administration of anesthetic drugs and to nociceptive stimuli (Jeanne et al. (2009)). A related technique is based on wavelet-based cardio-respiratory coherence, resulting in a normalized index that has been shown to respond to both nociceptive and anti-nociceptive events, Brouse et al. (2010). Both techniques are currently undergoing clinical trials for validation. One should also mention the Analgoscore$^{\text{TM}}$, a pain score derived from heart rate (HR) and mean arterial pressure (MAP) that has been used in closed-loop control.

An interesting method for assessing nociceptive reactions is based on the observation that a sudden electrocortical activation, e.g. demonstrated by an increase in BIS values, is a reflection of an inadequate analgesic state or level of antinociception. This principle has been used in the most clinically tested closed-loop controller for anesthesia.

3.3 Sensing for Neuromuscular Blockade

Monitoring of neuromuscular relaxation is performed by measuring, mostly by acceleromyography, evoked muscle response following supramaximal stimulation of the ulnar nerve. The standard stimulation consists of a train of four short pulses, and the level of paralysis is characterized by the ratio of the amplitude of the fourth response normalized by the that of the first one, the so-called T4/T1 ratio. Because of the virtual on/off nature of the measurement, it is not an ideal one for use in closed-loop control. Fortunately, fine control is not a clinical requirement. Nevertheless, new techniques are being developed based on phonomyography, which consists of recording low-frequency sounds created during muscle contraction, are being developed. The advantage of phonomyography is that it can be used at sites that are more clinically relevant than the adductor pollicis.

4. MODELLING FOR ANESTHESIA

Modelling of the distribution and effect of anesthetic drugs has traditionally been done using pharmacokinetic (PK) models for the former, and pharmacodynamic (PD) models for the latter. Typically, pharmacokinetic models are based on maxillary compartmental models, while PD models consist of a simple compartment followed by a sigmoidal nonlinearity. For propofol, a three-compartment is used, yielding the transfer function between the infusion rate I_p and the plasma concentration C_p:

$$C_p = \frac{1}{V_1}\frac{(s+z_1)(s+z_2)}{(s+p_1)(s+p_2)(s+p_3)}I_p(s)$$

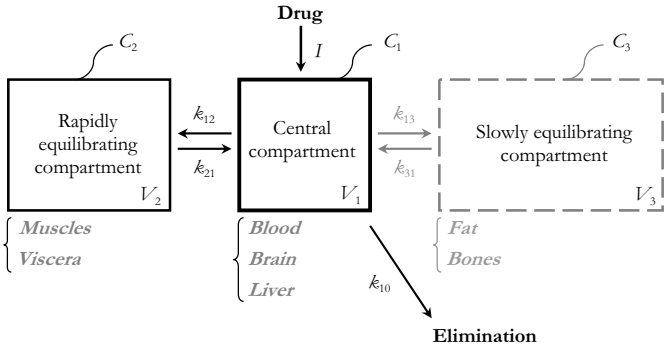

Fig. 1. A three-compartment PK model

The PD model is usually described by a transfer function between the plasma concentration C_p and the effect site concentration C_e

$$C_e(s) = \frac{k_{e0}}{s+k_{e0}}C_p(s)$$

followed by a Hill equation relating C_e to the effect:

$$E(C_e) = \frac{C_e^\gamma}{EC_{50}^\gamma + C_e^\gamma}$$

where EC_{50} denotes the effect site concentration corresponding to a 50% clinical effect and γ is the cooperativity coefficient. For remifentanil, most PK models involve only two compartments, resulting in a simpler transfer function.

Propofol and remifentanil are known to interact with each other in a synergistic fashion in their hypnotic/analgesic effect. (Kern et al. (2004)) This observation constitutes the basic assumption on which the balanced anesthesia concept is based on. Studies of the pharmacodynamic interactions between these two drugs have been limited to steady characterization through the use of response surfaces, which can the be parameterized, e.g. as:

$$E(v_p, v_r) = \frac{(v_p + v_r + \alpha v_p v_r)^\gamma}{(v_p + v_r + \alpha v_p v_r)^\gamma + 1}$$

where v_p and v_r are respectively the effect site concentrations of propofol and remifentanil normalized by their EC_{50}, and $\alpha > 0$ characterizes the synergy between the two drugs. Note that the interaction is equivalent to the use of a new fictitious drug $v = v_p + v_r + \alpha v_p v_r$.

While pharmacokineticians and dynamicists strive to improve the accuracy of PKPD models by introduction of a number of covariates in an attempt to reduce the uncertainty of TCI systems, a number of studies have shown that in order to develop a clinically satisfactory closed-loop control systems, simpler models such as first-order plus delay have the same level of predictive power.

5. CONTROL OF ANESTHESIA

5.1 Control Paradigm

After ensuring a fast and safe induction, the anesthesiologist needs to maintain the patient in an adequate state of hypnosis, analgesia and paralysis according to the requirements of the surgical procedure. The anesthetic and opioid titration needs to be constantly adjusted in order

to avoid both under and overdosing of the patient. The idea of an automated system that would regulate drug dosing to maintain the adequacy of the anesthetic regimen is thus natural. Closed-loop anesthesia would not replace the anesthesiologist, but would allow them to concentrate on higher level tasks.

A closed-loop controller for anesthesia should induce the patient rapidly, but with minimal overshoot and then maintain the patient in an adequate state of anesthesia and analgesia at least as well as an expert anesthesiologist. Translating this in control specifications is difficult, but for a BIS-like index, it could be translated into a rise time at induction of 3-4 min, with overshoot less than 10-15% and a good damping ratio of at least 0.7. During maintenance a BIS-like index should stay about 85% of the time within 10 points of the target. Control of analgesia should be such that in case of arousal (which in control engineering terms can be thought of as an output disturbance), the patient response is rapidly suppressed, say within 2 min and without inducing oscillations. The clinical outcome should be improved hemodynamic stability, faster emergence, and possibly reduced drug consumption. The main challenge is the inherent variability, both inter-patient and intra-operative, thus robust stability and performance are paramount.

5.2 Historical Period

The first efforts to automate anesthesia go back to the work of Mayo and Bickford in the early 1950's with their attempts to develop EEG-based automatic delivery of volatile agents, see e.g. Bickford (1950). What follows is by no means an exhaustive review of the published work on closed-loop control of anesthesia. Closer to us, in the 1980's a significant amount of work was performed on end-tidal concentration control for inhaled anesthetics such as halothane (see e.g. Westenskow et al. (1986)); closed-loop control of neuromuscular blockade (see e.g. Brown et al. (1980)) or mean-arterial pressure control (Monk et al. (1989)). In 1989, Schwilden (Schwilden et al. (1989)) published the first work on closed-loop delivery of proposal guided by the EEG median frequency. during a study on 11 healthy volunteers. For a review of the progress from 1949 to 1980, see Chilcoat (1980).

5.3 The Last Two Decades

The advent of the BIS monitor in the mid-1990's dramatically changed the situation, resulting in a significant increase in the number of studies, both simulated and clinical on closed-loop control of anesthesia, particularly of depth of anesthesia.

One of the earliest efforts by engineering groups was on the control of BIS during isoflurane, a system that was tested clinically on humans volunteers during minor surgical procedures, (Gentilini et al. (2001b)). Their system consists of two cascaded loops, the slave one being in charge of isoflurane end-tidal concentration that receives its set point from the master loop in charge of maintaining the BIS value between 40 and 50. Both controller are model-based Internal Model Controllers (IMC). The system behaved satisfactorily during those clinical tests. The patients however, were induced manually, the controller taking over only for the maintenance phase. That group also considered control of mean arterial pressure by closed-loop control of alfentanil using a PKPD model-based explicit predictive controller with constraints, Gentilini et al. (2002). Here too, successful clinical tests were performed. These two systems were combined for joint control of hypnosis and analgesia during successful clinical tests, (Gentilini et al. (2001a)).

Early efforts of BIS-guided closed-loop control of propofol infusion were performed by Absalom et al. (2002); Absalom and Kenny (2003) who used a PID controller tuned in a very ad-hoc manner to adjust the propofol effect site concentration setpoint in a target site infusion system. This was clinically tested on 20 patients. Not surprisingly, the performance varied significantly from patient to patient, the system displaying instability for some of them. All patients were induced under TCI mode, with an effect site concentration chosen by the clinician who then switched to closed-loop control for the maintenance phase. A system with a similar structure is described in Liu et al. (2006). That controller is not exactly a PID controller, but a rule-based one that is very similar to a PD controller. After significant tuning, this system was tested against manual control in a randomized controlled trial involving 164 patients (83 in closed-loop). That system was shown to outperform manual control in terms of BIS variability, and resulted in similar hemodynamic stability. Puri Puri et al. (2007) describes a heuristically-tuned "adaptive" PID controller tested against manual control in a clinical trial involving 40 subjects. A similar system is described in Hemmerling et al. (2010) in which what seems to be a heuristic set of rules emulating a PD controller is tested against manual control in a clinical trial involving 40 subjects. Both studies report similar results and are remarkable in the lack of a detailed description of the control algorithms.

Because those three systems were designed heuristically, their theoretical properties are difficult, if not impossible to assess. A rigorous approach to robust PID tuning for anesthesia is described in Dumont et al. (2009) where a PID controller is robustly tuned for a population of 44 adults. Results of a feasibility study in adults showed that this simple controller provided adequate anesthesia (Dumont et al. (2011)). This led to the development of a similar system for pediatric use, whose results in a pilot study are reported in Soltesz et al. (2012), van Heusden et al. (2012) and West et al. (2012). Although preliminary results seem to indicate that a robust PID controller manages relatively well with the significant interpatient uncertainty in a pediatric population, a patient-individualized has been proposed and shown, so far on simulations only to outperform a population-based controller (Soltesz et al. (2011)).

In Liu et al. (2011), the authors present what they term a dual loop that manipulates both the propofol and remifentanil infusion rates based on the BIS alone. The basic idea is that sudden increases in the BIS index are due to a nociceptive reaction and reflect an inadequate analgesic state. The controller that manipulates the remifentanil is a combination of a proportional action and a number of heuristic rules. Randomized clinical trials involving 167

patients on a wide variety of procedures showed that the system provides better control of the BIS than manual control, similar hemodynamic stability accompanied with increased remifentanil consumption. This system, like its predecessor induces the patient in TCI mode, with manually set targets for both propofol and remifentanil effect site concentrations. The same group (Liu et al. (2012)) recently extended its control system using the M-Entropy monitor to the control of both the depth of hypnosis as measured by the State Entropy while using the difference between the Response Entropy and the State Entropy as a measure of nociception. In a clinical study involving 61 subjects, conclussions similar to their BIS-based system are drawn. Hemmerling (Hemmerling and Charabti (2009)) describes a system that he calls McSleepy controlling depth of hypnosis based on the BIS, analgesia based on his Analgoscore, and muscular relaxation using phonomyography. Although McSleepy is reported to provide adequate anesthesia, little technical details and clinical results are publicly available. In Janda et al. (2011), combined control of BIS-based depth of hypnosis and muscular relaxation based on electromyography using decentralized MIMO control (Simanski et al. (2009)) is tested on 20 patients during maintenance of anesthesia. For neuromuscular blockade, a generalized predictive controller (GPC) is used while for depth of hypnosis, a fuzzy proportional, differential plus integral attempts to maintain a target of 40, and said to be "able to maintain the target values with a high level of precision in a clinical setting".

Many studies have also been performed by academic engineering groups, in order to explore the suitability of a number of control techniques: e.g. robust predictive control (Ionescu et al. (2008)), model-predictive control (Sawaguchi et al. (2008)), nonlinear adaptive control (Haddad et al. (2006)), neuro-fuzzy control (Mahfouf et al. (2005)), bayesian adaptation (de Smet et al. (2008)), L_1 adaptive control (Ralph et al. (2011)).

5.4 The Future

Despite the number of studies that have over the years demonstrated the feasibility and safety of closed-loop control of anesthesia, the regulatory hurdles abound before it can be approved for routine clinical use, (Manberg et al. (2008)). First and foremost the clinical benefits of those systems have to be clearly demonstrated , and this will require extensive multicentric clinical studies involving tens of thousands of patients. Many of the systems that have been used clinically so far have been developed without control engineers and consist of very heuristic controllers. This is important for control experts to be at the heart of the design of those systems to ensure they are based on sound control theory, as regulatory approval will likely require guarantees in terms of stability, robustness and performance. It is not clear what level of control complexity is required to achieve clinically acceptable performance. Novel monitors of nociception are in the works and will allow real multivariable control of hypnosis and analgesia. It is also important to realize that the systems discussed here only consider a subset of what an anesthesiologist needs to do to ensure patient safety. Other systems, e.g. for hemodynamics and fluid management are being considered and should undergo clinical trials in the coming years.

6. CONCLUSION

The development of closed-loop control of anesthesia has been a long road, the first attempts having been made over sixty years ago. Despite the recent progress in sensing and the number of successful clinical trials, the field is far from having any significant impact on clinical practice. For the technology to mature and become clinical reality, closed cooperation between control engineers, clinicians, medical device manufacturers and regulatory bodies will be required.

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