Clinical Anesthesia and Control Engineering: Terminology, Concepts and Issues

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***Abstract*—The anesthesia community has recently witnessed numerous advances in the monitoring of the anesthetic state. This development has spurred a renewed interest in the automation of clinical anesthesia. While this subject was the apanage of researchers with strong clinical background, recently the control community became also involved. The collaborative studies which resulted have proven the feasibility of feedback-controlled anesthesia systems, while stressing out the many challenges this field imposes. This paper addresses its specificities in a familiar context for control engineers. Anesthesia concepts and terminology, monitoring issues, as well as drug properties and mechanisms of action, are covered. Prior attempts at closed loop anesthesia are reviewed.**

***Index Terms*—Balanced anesthesia, hypnosis, analgesia, antinociception, closed loop anesthesia.**

I. Introduction

PARADOXICALLY, surgeons achieve healing by first inflicting injury. Anesthesiologists use general anesthetics to prevent the awareness of pain and attenuate the body's "stress" response to injury. The unconsciousness produced by general anesthesia is accompanied by a depression of the respiratory (e.g., hyperventilation), cardiovascular (e.g., increased heart rate and blood pressure) and endocrine responses to surgery. Since the degree of surgical stimulation changes during surgery, anesthesiologists must constantly adjust the extent of anesthetic depression to avoid both under- and overdosing. Otherwise, excessive activation of the sympathetic nervous system or pharmacological depression could in turn lead to injury of critical organs, especially in patients with limited respiratory and cardiovascular reserves. As a result, cardiorespiratory monitoring and treatment strategies during anesthesia parallel the approach used to resuscitate critically ill patients in the intensive care unit.

Until the mid-20$^{\text{th}}$ century, only inhaled anesthetics were available to create the state of general anesthesia. However, their onset of action was slow and often accompanied by vomiting and signs of respiratory irritation. In the 1940s, the introduction of intravenous agents revolutionized the medical specialty of anesthesia, and over the past 50 years, further refinements in anesthetic pharmacology, equipment and technology have occurred. Nowadays, anesthesiologists have access to agents that can act within a minute of their administration and can block specific mechanisms such as cognition, awareness, memory, stress response and muscle movement. These agents are further characterized by their fast metabolism and elimination. Hence, constant monitoring of their titration is necessary to provide patients with an adequate drug regimen during surgery. Having an automated mechanism to control titration is appealing.

Control technology has been applied in a wide variety of industrial and domestic environments, improving performance, safety and efficiency. Anesthesia, a keystone specialty in the field of medicine, has not yet benefited from such technological advances. Due to the lack of knowledge of the anesthesia underlying mechanisms and the large intra- and inter-patient variability, no appropriate conventional control framework could yield up to now satisfactory results in a clinical setting. However, recent advances in sensing devices, along with robust nonlinear control theories, have generated new hopes that the gap between manual and automated control of anesthesia could finally be bridged, at least at the regulatory level.

This paper presents aims at allowing control engineers to familiarize with clinical anesthesia and with the specificities of this field. A short introductory section will present the concepts and terminology in use. Aspects of today's practice such as the conduct of anesthesia and the risks and outcome of anesthetic procedures will also be discussed.

The issue of Depth Of Anesthesia (DOA) is then tackled, and a review of the different techniques available today is provided.

Since the drugs are the actuators by which anesthesiologists drive their patients into an adequate anesthetic state, this tutorial would not be complete without introducing the extensive pharmacopoeia from which they select the appropriate combination of agents.

Finally, we will conclude this paper by discussing the rationale for automation in clinical anesthesia. With this opportunity, prior attempts at closed loop control of anesthesia will be briefly reviewed.

II. Anesthesia: Concepts, Terminology and Issues

A. Functional Components of Balanced Clinical Anesthesia

Although the scientific definition is uncertain, clinical anesthesia has been described as a state of "drug-induced unconsciousness, [where] the patient neither perceives nor recalls noxious stimuli" [1]. This functional definition as proposed by Prys-Roberts in 1987 limits general anesthesia to an absence of both conscious awareness and memory formation (i.e., *hypnosis* and *amnesia*). In other words, it does not describe the absence of unconscious reflexes to noxious stimuli (i.e. suppression of spinal cord reflexes

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leading to *areflexia* or *immobility*), nor the suppression of autonomic reflexes involving both the sympathetic and parasympathetic nervous system leading to cardiorespiratory control. Since drugs with analgesic properties are particularly effective at controlling these cardiorespiratory responses during general anesthesia, this last component is generally referred to as either *analgesia* or *antinociception*. Note that while many authors refer to this component as analgesia, we prefer the term antinociception, since analgesia implies the conscious perception of pain. It is therefore common in the literature to consider that the state of general anesthesia results from the combination of three functional components, that is, hypnosis, analgesia/antinociception and areflexia/immobility. While this *anesthesia triad* [2] conceptualization is somehow simplistic, most engineering-oriented authors contributing to this field are setting their work within this framework.

Following Prys-Roberts' definition, all anesthetics are hypnotics. They first act at the level of cognitive functions (cortex) by rendering patients unconscious. Inhalational anesthetics are ambivalent in their role as they are also strong analgesics, conversely to intravenous agents which are mainly hypnotics. However, note that with increasing doses of a hypnotic drug, it is possible to go beyond hypnosis and blunt the response to noxious stimuli, thus providing some level of analgesia and, indirectly, areflexia. As such, until the 1940s, it was common for anesthesiologists to use a unique agent at high concentration to achieve adequate anesthesia. Unfortunately, using higher doses usually results in stronger side effects during surgery (ventilation depression, cardiac arrhythmia, etc.), as well as during recovery (nausea, vomiting, etc.).

To alleviate undesirable side effects George Crile advocated in 1911 the use of local analgesics as a complement to light general anesthesia. In 1926 the term of *balanced anesthesia* was introduced by John Lundy to describe a combination of agents that would achieve adequate anesthesia. This concept can be well-understood when considering that analgesia and areflexia can be achieved using drugs such as *opioids* and *neuromuscular blocking agents* (NMBs), which can blunt specific mechanisms within the nervous system. These drugs are not hypnotics in the sense that they do not provoke unconsciousness (even though opioids do alter sensory and cognitive functions). Nowadays, the focus in clinical anesthesia is to achieve an adequate balanced anesthetic state using a combination of hypnotics (inhalational/intravenous anesthetics), opioids and NMBs. This technique has the advantage that much lower concentrations of drugs need to be administered, thus considerably reducing side effects and shortening recovery time. Balanced anesthesia is now the standard in the management and conduct of clinical anesthesia.

B. Risks and Outcome in Anesthesia

B.1 Mortality rate

The development of the anesthesia practice since the 19^{th} century arose mostly from concerns about patients' safety. Nowadays, clinical anesthesia is probably one of the safest components of any surgical operation. A 1986 survey [3] revealed that the overall death rate attributable directly to anesthesia was 1:185,056. This very low mortality rate can be attributed mainly to the equipment that monitors patients' vital signs, and eventually warns the practitioner of possible complications. Modern equipment is fairly sophisticated and includes standard devices such as Mass Spectrometers, Capnographs, Pulse Oxymeters, heart rate and blood pressure monitors, etc. Another aspect contributing to the increased safety is the availability of an extensive pharmacopoeia from which anesthesiologists can select an appropriate combination of drugs according to the patient status (e.g. medical records, allergies, age, etc.) and the type and duration of the operation.

Human error is probably the most common cause of death (hypoxic gas mixture, airway obstruction, errors in drug administration, lapses in vigilance, etc...) [4]. According to a 1987 study [5], 75% of anesthetic related deaths were due to the anesthetist' failure to apply life saving knowledge, while only 1.7% of cases involved equipment failure. Also, where the most cited reason leading to such events used to be overdosing (1960–1969), it is nowadays the inadequate preoperative preparation and patient' assessment that is the most cited error in anesthesia management. Finally the actual trend of increased efficiency in the operating room, so called *production pressures*, increases anesthesiologists' fatigue and might provoke misjudgement, resulting in reduced patients' safety.

B.2 Intraoperative awareness

While patients' safety is still an important issue, new concerns arose from the use of NMBs in the 1940s. These drugs block muscle movement and reduce muscle tone to facilitate surgery, but have the unpleasant consequence of obtunding the usual signs of light anesthesia. In modern practice, it is possible for a patient to exhibit the appearance of an adequate anesthetic state while being fully aware of his/her surroundings, and experiencing in its fullest the trauma caused by the surgery [6]. This event is referred to as *intraoperative awareness*. While not lethal, awareness with pain during surgery results in deep psychological consequences. These cases are fortunately extremely rare (about 0.01% [7]) and result principally from faulty equipment or human error.

Limited intraoperative awareness without presence of pain is more common, mostly when patients are maintained in a shallower depth of anesthesia or during emergencies. A number of such cases has been reported in the literature. Surveys have shown that patients experience explicit awareness between 0.2% and 1.6% of surgical operations [8], depending on the type of surgery (this figure can be much higher for procedures carried out on patients with major trauma during emergencies). While the conscious perception of pain is a rare event, patients suffer mostly from the anxiety and fear of experiencing pain. Event though in the large majority of anesthetic procedures patients do not have explicit recall of intraoperative events, it is estimated that they are able to respond to ver-

bal command at some point during general anesthesia in about 80% of cases [9].

The development of monitoring tools to assess whether patients are unconscious or properly *hypnotized* has been the focus of intense research ever since [10]. Note, that a study by K.B. Domino in 1999 [11] has revealed that the contribution of intraoperative awareness to professional liability in anesthesia is small. Based on a thorough review of 4,183 claims involving malpractice in anesthesia in the U.S. since 1961, only 1.9% of such cases were related to awareness. This study also showed that risks of intraoperative awareness were higher in women, and when using opioids and muscle relaxants with low - or no - volatile agent.

III. Measuring Hypnosis and Analgesia

Hypnosis and analgesia are the result of different mechanisms. Although it is not possible to measure them directly (i.e., the antinociceptive effect of the drugs), some physiological signs are sufficiently correlated to be adequate surrogate measures. For instance, it is believed that cortical activity mirrors the patient state of hypnosis. The fact that the brain can or cannot process sensory information can be observed in the *electroencephalogram* (EEG).

A. The EEG as a Measure of Hypnosis

The effects of anesthetic drugs on the EEG have been known since the early 1940s when neurophysiologists observed that the EEG of anesthetized patients contain slower waves with higher amplitudes. A number of techniques have been used to extract univariate features that quantify the hypnotic component of anesthesia. Some of these techniques are briefly discussed here. For a more in-depth look, please refer to Zikov [12].

A.1 Power Spectrum Analysis

With the development of microprocessors and signal processing tools, researchers have focused their attention on Fourier analysis of the EEG. Power spectrum analysis is used to obtain a frequency distribution of the EEG. Hence, any change in the frequency content of the signal can be visualized. Pichlmayr et al. [13] have published a thorough review of the effect of the different anesthetic agents on the EEG spectral distribution. It is common practice to distinguish between 5 frequency bands: δ band (0.25 Hz - 3.5 Hz), θ band (3.5 Hz - 7.5 Hz), α band (7.5 Hz - 12.5 Hz), β band (12.5 Hz - 32 Hz), and γ band (32 Hz - 70 Hz). For a normal awake patient, the EEG activity is principally concentrated in the δ and α bands. With increasing level of anesthetics, the activity of the alpha band tends to reduce, while the low frequency content of the delta band is increased.

To quantify the effect of anesthetics onto the EEG, researchers have tried to derive univariate indexes based on Fourier analysis and the resulting spectral distribution. Among the parameters that have been thoroughly investigated, we can mention the following two:

i. The Median Edge Frequency (MEF), the frequency that splits the power spectrum distribution into two parts of equal power, is advocated and used for closed loop control by Schwilden and co-workers ([14], [15], [16] and [17]).
ii. The Spectral Edge Frequency (SEF), the frequency below which 95% of the EEG power is present and proposed in 1980 by Rampil et al. [18], is said to be highly repeatable, but at the expenses of large inter-subject variations.

A.2 EEG modelling

The idea of modelling the EEG using auto-regressive (AR) techniques dates back to the early 70s until more recent application to anesthesia ([19]). As opposed to univariate descriptors, auto-regressive modelling generates a set of parameters that can further be correlated to the anesthetic depth. Neural networks can be trained in order to derive a single index from the AR parameters. Sharma et al. [20] have shown that this technique can lead to accurate results, at the expenses of a large network.

A.3 Bispectral Analysis

Recently, it has been argued that anesthetic agents tend to synchronize the generation of postsynaptic potentials [21], resulting in slower waves of higher amplitude in the EEG. For light anesthesia, additional lagging of some of the frequency components of the EEG is expected. This change in latency is not observable by spectral analysis as phase information is usually discarded. Standard spectral parameters fail to characterize sedative states, which in turn reduces their therapeutic window.

Conversely, bispectral analysis is a technique that can track changes in signal latency. Ning et al. [22] were the first to apply bispectral analysis to EEG in order to characterize sleep patterns in rats. They realized that there was a strong coupling between the frequencies of 6 and 8 Hz during Rapid-Eye Movement (REM) sleep. Sleep patterns being close to patterns obtained during anesthesia procedure, Ning assumed that this technique might lead to interesting results in monitoring the depth of anesthesia. Their assumption was validated in 1990, when Kearse et al. [23] reported that the bispectral index was more accurate than the spectral edge frequency for anesthesia induced by opioids (alfentanil and sulfentanil). These findings were confirmed by various authors ([24], [25], [26]).

Probably the most interesting result was obtained by a research team from Aspect Medical Systems Inc. who derived no less than 33 variables (bispectrum, bicoherence index, power spectral values) and combined to derive a single index [27]. In comparison with other methods (SEF, MEF, etc.), the accuracy of the index was significantly higher. Each individual variable was weighted according to data collected over 160 standard surgical procedures. Based on these findings, Aspect Medical Systems Inc. developed a monitor of consciousness in 1996. A single channel EEG signal is recorded through contact electrodes placed on the patient's forehead. An index representing the level of hyp-

nosis, and scaled between 100 (awake) and 0 (deepest hypnotic state), is calculated and displayed on the monitor screen.

A.4 Wavelet Analysis

While the bispectral index provides anesthesiologists with a reliable and highly repeatable index of hypnosis, its technology introduces a large inherent delay that reduces the performance expectations of any closed loop controller relying on this feedback variable. Recently, a technique that uses wavelet analysis of the EEG has been proposed by our research group in an attempt to solve some of the problems inherent to the bispectral technique [28], [29] and [12]. The wavelet transform is a computationally effective signal processing method particularly well-suited for extracting information from biological signals. It has been proved that the wavelet coefficients derived from the EEG are statistically representative of the patients' hypnotic state. The wavelet index compares well with the bispectral index, while offering a reduced computational complexity and a faster reaction to transients in patients' consciousness levels. A clinical trial has also shown that the wavelet method is more consistent than the bispectral technique [30] [31].

A.5 Evoked Potentials

Somatosensory information provoked by auditory, visual, or tactile stimulation generates transitory, oscillatory signals within the EEG itself. Such transient signals, if properly analyzed, can reveal information concerning patients' state of consciousness ([32], [33], [34], [35], [36]). For instance, *midlatency auditory evoked potentials* (MLAEP) have a very distinct shape depending on the subject being awake or asleep. The most remarkable feature beside the change in amplitude of the signal is the change in latency of some of the waves. A very interesting work by Huang et al. [37] has shown that it is possible to measure the hypnotic depth of a dog under anesthesia by using the wavelet transform of the MLAEP signal and feeding the wavelet coefficients to a properly trained neural network.

Although a significant amount of work has been carried out in this particular field, no real breakthrough has yet been achieved. A major disadvantage of using evoked potentials is their very low signal to noise ratio, which makes them particularly difficult to acquire, as they are embedded inside the EEG signal. New techniques such as wavelet de-noising have been successfully applied to partially alleviate this problem [38]. This method is still not practical as it introduces a considerable lag.

B. Measuring the Antinociceptive Effect

The measurement of antinociception is part of the critical care given by anesthesiologists in their daily practice. Surgical trauma is usually accompanied with strong sympathetic and parasympathetic activity (e.g., heart rate and blood pressure changes, sweating, lachrymation, somatic movements, etc.).

Deriving descriptors of antinociception that can be used as feedback quantity is a challenge. For instance, blood pressure alone is not a reliable measure, as other parameters such as blood loss and the action of vasoactive drugs can affect the cardiovascular system. As a result, the analgesia functional component hasn't yet received enough attention. In recent years, only a few monitors have been introduced, without full disclosure of their scientific base.

B.1 The EEG as a Measure of Analgesia

The effect of opioids onto the EEG has been thoroughly investigated. In 1984, Smith et al. [39] concluded that the EEG probably reflects the depth of anesthesia with high-dose narcotics. Later studies by Scott et al. ([40] and [41]) resulted in similar conclusions. The same techniques (MEF, SEF, BIS) described previously can be used for measuring the effect of opioids as well. However, the therapeutic window of these techniques is limited.

B.2 Heart Rate Variability as a Measure of Analgesia

Heart Rate Variability (HRV) is a rather new technique. Two monitors are presently commercialized (Anemon I, Medical Control System SA, and Fathom, Amtec). The concept of heart rate variability reflects that under painful stimuli, respiratory patterns fluctuate. This fluctuation, usually referred to as *sinus arrythmia*, is difficult to measure. However, it strongly correlates with fluctuation of the cardiac rhythm. Observing the changes of the interval between R-waves of the electrocardiogram forms the basis for this measurment. Different techniques have been used to achieve this endpoint ([42] and [43]), however, no extensive clinical trials have been carried out to validate their efficacy.

IV. An Extensive Pharmacopoeia

Anesthesiologists act through the administration of a combination of anesthetics, opioids, and eventually, NMBs. These drugs, even when taken within a same family, have different properties. Familiarity with these drugs is therefore essential for control engineers to allow an informed choice of the most promising ones for close loop control.

A. Anesthetics

A.1 Inhalation Anesthetics

With the advent of fluorine technology in the 1940s, new inhaled anesthetics were developed. As compared to ether and chloroform, fluorine compounds have lower blood solubility (thus ensuring rapid induction and recovery), lower toxicity, are less irritating for the airway, and not flammable. Nowadays three agents are commonly used in combination with nitrous oxide: isoflurane, desflurane and sevoflurane. All these agents provoke a decrease in mean arterial blood pressure and an increase in heart rate when administered to healthy subjects. A tendency to depress ventilation, hence to allow more carbon dioxide to accumulate in the blood, is also a common side effect, see

[44]. Other similar gases such as halothane and enflurane were also developed, with a limited use to specific cases.

A major advantage of inhaled anesthetics is that the drug uptake in the arterial blood stream can be precisely titrated by measuring the difference between the amount of gas administered to the patient and the amount of gas expired. This measurement can be done in real-time using a mass spectrometer. As a result, inhaled gases are used extensively to maintain a desired depth of anesthesia.

A.2 Intravenous anesthetics

The idea of injecting a drug directly in the blood stream goes back as far as the 17^{th} century. However, intravenous anesthetics started to be used only in the late 1930s after the development of hexobarbitone by Helmut Weese in 1932 and thiopentone by Waters and Lundy in 1934. The rapid induction and short duration obtained through these agents opened a new era in anesthesia (for a detailed discussion of Weese and Lundy's discoveries, refer to [45] and [46]). However, few years after their introduction, and due to the poor understanding of their mechanism of action, intravenous agents were used similarly to inhaled anesthetics (i.e. as the sole agent during anesthesia). Furthermore, barbiturates are short acting drugs. To maintain a prolonged desired effect, they were administered as large boluses. The administration of thiopental and hexobarbitone in such a manner to the hypovolemic casualties of Pearl Harbor resulted in so many deaths that intravenous anesthetics were described as an "ideal method of euthanasia". It is only with the revival of the balanced anesthesia concept that intravenous anesthetics were reintroduced in clinical practice.

Intravenous anesthetics can be classified into 5 families: Barbiturates, Benzodiazepines (midazolam, diazepam, lorazepam), Phencyclidine (ketamine), Carboxylated imidazole (etomidate), and Isopropylphenol (propofol). Compared with volatile agents, intravenous anesthetics (beside ketamine which retains a particular status) do not provide analgesic effects at normal clinical concentration, hence, are typically hypnotic drugs. However, opioids and intravenous anesthetics, when used in combination, are strongly synergetic, both in terms of hypnosis and analgesia.

Propofol, introduced in the practice in the early 1990s, has become the intravenous drug of choice in the anesthesia practice. One particular characteristic of propofol is its fast redistribution and metabolism. As a result it can be easily used in infusion schemes as it provides very fast emergence, without cumulative effect.

B. Opioids

Opioids are unique in the sense that they provoke analgesia without loss of touch, temperature and consciousness, when administered in small doses.

Opioids act as agonists at specific receptors within the Central Nervous System (CNS) and in peripheral tissues outside the CNS. Their principal effect is the inhibition of neurotransmitter release, resulting in a significant analgesic effect. Opioids are best used before painful stimuli occur (i.e., preemptive analgesia). It is interesting to notice that all opioid agonists produce dose-dependent depression of ventilation. When administered as large boluses, opioids induce apnea. As a result, and during anesthesia, artificial ventilation must be used to avert hypoxia. Other common side effects are nausea, vomiting, constipation and physical dependence.

Contrary to most anesthetics, opioids are known to have a very good hemodynamic stability, and are thus particularly suitable for cardiac anesthesia. Opioids can produce unconsciousness when used in very large doses. This observation has led some authors to believe that opioids should be considered to be anesthetics, as they fit Prys-Roberts' definition [47]. However, the state of unconsciousness brought by opioids is not reliable. It has been shown for instance that they cannot fully replace inhalational gas to provoke an adequate state of hypnosis. However, their use can reduce the requirements of any inhalational gas by up to 50% [48]. Also, the sedative effect of opioids is opposed by the presence of acute pain. Hence, even though patients in severe pain receive very large amount of opioids, they can remain fully alert. In current practice, opioids are almost always supplemented by other anesthetics.

Mainly 5 opioid compounds are used in today's practice: morphine, fentanyl, sufentanil, alfentanil, and remifentanil. While they all have similar effects, their characteristic differ tremendously due to their large differences in lipid-solubility property. Of particular interest is remifentanil, a new agent introduced in the practice in the mid 1990s. Its potency is twice that of fentanyl and its effect-site equilibration time is slightly less to that of alfentanil (about 1.1 min). It differs from other opioids by its molecular structure. Its ester linkage renders it susceptible to hydrolysis. This property results in its rapid degradation in inactive metabolites [49]. The main characteristics of remifentanil are: brevity of action, rapid onset, noncumulative effects in inactive tissues, and rapid recovery after termination of the infusion. As a result, its context-sensitive half-time is independent of the duration of the infusion. The risk for post-operative rebound of effect, which is common with other opioids, is greatly reduced. Remifentanil is used mostly to supplement the analgesic component of general anesthesia. Its brevity of action gives anesthesiologists the ability to help their patients to recover rapidly from undesirable opioid-induced side-effects such as the depression of ventilation.

C. Neuromuscular Blocking Agents

Neuromuscular blocking drugs act locally at the level of the neuromuscular junction by interrupting the transmission of nerve impulses. Their principal use is to produce skeletal muscle relaxation to facilitate intubation and to provide optimal surgical condition. NMBs do not have any analgesics nor hypnotic properties. They also do not interact with opioids and anesthetics. Succinylcholine is used whenever a short duration of action is needed. Derivatives of curare (e.g. mivacurium, rocuronium, pancuronium, etc.) can also be used when a longer effect is desired.

D. Inhalational Anesthetics vs. Intravenous Agents

Inhalational anesthetics are considered by many practitioners as near ideal anesthetics as they have both an hypnotic and an antinociceptive effect. This explains why many closed loop anesthesia attempts have been done using inhalational anesthetics as the sole actuator. Combined with the fact that blood concentration of inhalational anesthetic is readily available, this considerably can simplify the control problem, since additional states are measurable.

Conversely to inhaled anesthetics, the arterial blood concentration of an intravenous drug cannot be readily measured. As a result, the titration of these drugs is more difficult as the anesthesiologist does not have any feedback on how much of the administered drug has been metabolized or stored in inactive tissues. In the majority of cases, intravenous agents are given as large boluses for the induction of anesthesia, while maintenance is ensured by inhalational gases. However, since intravenous agents are more specific than inhalational anesthetics, their use give more flexibility in controlling separately the functional components of anesthesia. Also, the control of infusion pumps to administer intravenous drugs is easier as compared to the control of a vaporizer which introduces complex nonlinear dynamics in the system [50].

V. Automation in Clinical Anesthesia

A. Drugs: Action, Effect and Interaction

The development of safer and more potent agents with faster onset of effect and, in certain cases, shorter duration of action, has greatly impacted anesthesia practice. Nowadays, small drug quantities used in combination can produce a balanced state of anesthesia while minimizing side effects.

Inhalational gases are still the background anesthetic agents on which standard practice is based. However, intravenous agents are increasingly employed in the operating room. Currently their administration is geared towards facilitating intubation, compensating for undesirable changes in patients' state and also in anticipation of painful surgical stimuli. In this realm the short acting characteristic of intravenous agents such as remifentanil and propofol indicates that these drugs should best be used in infusion regimens, since their administration as boluses often result in too strong effects for too short periods of time.

The inability of measuring intravenous drugs plasma drug concentration raises questions. Currently this issue affects the ability of the anesthesiologists to set precise rates of infusion. The result is that they usually rely on experience, as well as on infusion regimens published in medical journals. Such state estimations is prone to error, and the resulting titration might not correspond to patients' real needs.

Finally, in the context of closed loop control, and when using intravenous drug as prime actuators, it is necessary to account for both patient variability and drug synergism:

- Patient variability results from differences in the way the drug distributes and is eliminated from the body (renal and liver function, cardiac output, patient's age, lean body mass). Genetic differences and enzyme activity might also alter the mechanism of action of the drug. While some patients might be hyporeactive (e.g. acute tolerance due to addiction), in some cases hypersensitivity can be observed for patients having allergy to a given drug.
- When using different drugs in combination - such as in the context of anesthesia - interactions can be observed. An *additive* effect signifies that a second drug taken concurrently with a first will produce an effect equal to the superposition of their effects (e.g. the anesthetic effects of two inhaled anesthetics are additive [51]), whereas a *synergistic* effect means that the resulting effect is greater than what could be expected from superposition. Synergism often appears when using hypnotics in combination with opioids. In some particular cases, drugs can also be *antagonistic*, as they tend to counter-act each others when administered concurrently (e.g. an opioid and its antagonist). From a control point of view, such interactions between drugs tend to generate an important cross-coupling. Only very few models of such coupling have been discussed in the literature ([52] [53] and [54]). These models are mainly mathematical expressions that describe drug interaction in steady state.

B. Monitors: Relevance, Dynamics, Bandwidth and Reliability

Measuring the state of anesthesia is still a grey area. Advances were made towards the use of the electroencephalogram, usually in its processed forms (e.g. bispectral index, wavelet index, auditory evoked potentials), for correlated measures of consciousness. Some interesting work has also been done in the field of analgesia monitoring where surrogate measures have shown some potential. Nevertheless, the major problem faced by most of these sensors is the established correlation accuracy between their output and consciousness. Expensive studies were made to demonstrate such properties, but the reality is that only directly measurable vital signs have a true meaning. Such measurements are in fact the ones used by anesthesiologists in their practice, so the natural question is "Why use anything else?". The argument that favors the use of surrogate measures is their ability to remove delays and time constants from the normally used vital signs. This happens at the expense of a continuous scientific debate, which is further emphasized by the existence of sensors working better than others when it comes to the estimation of the anesthetic state. Gradual responses, backed by a reduced delay and time constant in the determination of the consciousness/analgesia level will favor the use of that particular sensor.

Another limiting factor on current sensors is their sampling frequency. The performance limitations generated by a slow sensor can be overwhelming, leading to the controller inability to correct for fast transients.

Sometimes, and more important than the accessability of the measurement, is the reliability of the sensor in the rough environment of the operating room where the sensor needs to cope with artificially created (e.g. electrocautery, x-ray, movement) and patient generated (e.g. muscular, neural) artifacts. Surrogate measures can also be influenced by other factors such as the administration of other drugs (e.g. premedicants), blood loss, etc., which will result in an unreliable measure. It is therefore mandatory to establish a therapeutic window and normal working conditions for each sensor.

All these issues give reasons to spend significant effort toward improving the sensors. The other direction of development is the combined use of surrogate measures with measurable vital signs for better estimation of the anesthetic state. Building such composite indices represents the direction currently taken by a number of research groups.

C. Models: Relevance, Accuracy and Complexity

Essential for closed loop control in a model based framework is the knowledge of the plant model. Artificial Intelligence (AI) type learning embeds patient modelling in fuzzy rules or weights of a neural network. As result, and no matter which path for control is taken, some knowledge of the patient model is required.

Typically, compartmental models capture the behavior of the patient to a number of external stimuli and drugs. Alternatively, a black box model can be used. In turn, gray box identification techniques estimate parameters in a physically based model structure. Most of the identified models are still limited to a univariate approach. Only in the last years, the concept of cross coupling, and hence of a multivariable model, has attracted the interest of researchers. Such an approach leaves room for the creation of new knowledge with direct implication in the accuracy of the control scheme.

Having a complex model that captures all nonlinearities in the system would be desirable. On another hand it is recognized by practitioners in control system theory that models for control need to be as complex as required by the control scheme employed. This means that for a reduced degrees of freedom in the controller, a complex model produced possibly at the expense of costly patient trials might not be necessary. Therefore, the complexity of the model should be linked to the complexity of the controller. This in turn should be governed by the closed loop performance requirements to be defined in the context of current sensor accuracy.

D. Control: Lessons From the Past

The concept and implementation of closed-loop anesthesia has been investigated for the past half century via numerous attempts at controlling anesthetic drugs titration through feedback control. A selected chronological survey of this prior art is summarized in Table I. For each mentioned attempt, we listed the feedback quantity, the drug used, and the control technique employed. In spite of a good number of such attempts, no clinically satisfying results have been obtained so far. This survey is also limited to attempts which focused more precisely on the control of hypnosis. Other work focusing on the control of heart rate and blood pressure, as well as the control of muscle relaxation in the context of anesthesia has not been reported here.

In the recent years researchers have been using either a simple PI or a lookup table of the drug pharmacodynamic model to set the target plasma concentration of a target controlled infusion devices in order to reach and maintain a given hypnotic reference. The successes reported by Struys et al. [55] and Absalom et al. [56] can be easily attributed to the fact that their system titrated the drug according to the index of consciousness provided by the bispectral monitor, instead of the performance of the closed loop controller itself.

The results produced by controllers embedding advanced techniques, as shown in the work by Frei et al. [57] and Gentilini et al. [58], emphasize that the problem is far from being solved due to the aforementioned challenges posed by the intra- and inter-patient variability. There have also been attempts at closing the loop by Linkens et al. ([59], [60], [61], [62]) using a variety of intelligent control techniques such as expert systems and fuzzy logic. Linkens et al. were probably among the first to attempt the control of distinct anesthesia components simultaneously (analgesia and areflexia) using different agents (atracurium and isoflurane). An in-depth analysis of such cases reveals the need for strong knowledge of the patient model. The intra- and inter-patient variability makes the establishment of a priori rules very difficult. From the perspective of interaction between drugs, and of particular interest, is the attempt by Zhang et al. in 1998 [63] at controlling an intravenous anesthetic (propofol) together with an opioid (fentanyl). This approach was limited to the control of the plasma concentration of propofol and fentanyl in dogs, where the setpoints were chosen to minimize the wake up time.

As an overall remark, it seems that, while the previous attempts were promising, the researchers lacked the proper tools to design controllers that completely account for patients variability and drug interaction. The results reported in the literature are involving a reduced size healthy population. As a consequence these closed loop achievements did not manage to convince practicing anesthesiologists about the viability of the proposed methods.

E. A point of view: flight control

To introduce the future research path taken by a number of groups, it is convenient to draw a parallel with automated flight control. The role of the anesthesiologist is similar to that of a pilot: after take-off (induction), the pilot usually maintains an adequate flight trajectory (hypnosis, analgesia/antinociception, areflexia/immobility). Nowadays such tasks are performed by flight controllers able to plan ahead, optimize fuel consumption and minimize the duration of the flight. In this sense closed loop anesthesia

is somehow similar since by changing the titration of intravenous drugs, the anesthesiologist can drive the patient into a deeper or lighter hypnotic and/or analgesic state, according to the requirements of the surgical procedure.

Using proper feedback quantities and drug models the possibility to automate the drug titration and to allow the practitioner to concentrate on higher level tasks seems viable. In keeping the comparison, closed loop anesthesia would not replace the anesthesiologist. On the contrary, the workload of the anesthesiologist will be reduced during the maintenance stage, leaving room for full attention in case of an emergency when the override of the controller will be still required.

An experienced person in both the aeronautic and anesthesia field can advocate that such a comparison is a bit forced. Our view is that having access to both worlds can be a good way to understand in what sense flight controllers and anesthesia autopilots are different, and hence determine the challenges faced by a potential anesthesia closed loop system. Addressing such issues is the main problem left unsolved before the prototype of an anesthesia controller design is handed to industry for large scale implementation and commercialization.

VI. Conclusion

Anesthesiologists have succeeded in making anesthesia a safe procedure. It is therefore natural to wonder whether automation in clinical anesthesia is a valuable research endeavor.

The reality is that, efforts in fast action drug development, sensor creation, robust nonlinear control complemented by changes in the current anesthesia practice, are paving the way to closed loop anesthesia control. We surmise that before the end of this decade conventional surgeries will be carried on under the supervision of an anesthesiologist or specialized nurse by such anesthesia autopilots. The cost and safety implications are huge, justifying the efforts of a number of research groups. In spite of a half century history, we believe it is only now that the critical mass has been reached. The opportunities available for research will go beyond the operating room in the direction of daily administration of drugs by portable devices.

Echoing Glass [64] [65] and Kissin [66] points of view, it is our belief that the control of anesthesia cannot be done based on a single feedback quantity. It is necessary to consider all of the anesthesia functional components when setting the controller specifications and requirements. To respect the current balanced anesthesia practice, a first step would be the control of both an hypnotic agent (e.g. such as an intravenous anesthetic) and an opioid, in order to reach an adequate anesthetic state. Such a system would be directly usable in most elective surgeries, where the use of neuromuscular blocking agent is not required.

From a control point of view, the challenges are numerous. First, such a controller will need to account for interpatient variability. Also, models linking the administration of drugs and their effects will need to be developed in a multivariable framework so as to account for the cross coupling introduced by their pharmacokinetic and pharmacodynamic interactions. Finally, the therapeutic window and the nonlinear nature of the sensors used to provide the feedback measurements will have to be included in the design. This nonlinearity comes from the steep dose/response relationship of the drugs in use today. It is also worth noticing that their effective to lethal relationship is amongst the closest of all known drugs, meaning that overdosing can have dire consequences. Clearly, the sensor issue is critical.

On the way to such high level goals, the purpose of current research projects is to investigate how modern multivariate nonlinear robust control techniques can be effectively applied to clinical anesthesia. It is believed that a closed loop system would precisely titrate infusion agents according to the patients' needs, resulting in lesser intra- and postoperative side-effects. In addition, by judiciously selecting the setpoints, the patient will be quickly driven into an appropriate anesthetic depth according to the requirements of the surgery and the anesthesiologist's judgement.

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Study	Feedback quantity(ies)	Controlled Agent(s)	Control Technique	Population	Comments and Limitations
Bickford et al., 1950–1960 [67] [68] [69]	EEG energy in the 4 to 12 Hz band	Pentothal or Ether	On/Off control	Rabbits, cats, monkeys. Clinical trial on 50 patients undergoing various abdominal surgeries	Oscillations due to the control technique. Method sensitive to extraneous interferences. No opioids have been administered concurrently, thus seriously limiting this technique in today's practice.
Bellville et al., 1955–1960 [70]	EEG amplitude in a defined frequency band	Cyclopropane	Analog control (P or PI?)	Not Disclosed	No results have been presented. The proposed technique is merely an improvement of Bickford's servo anesthesia. The authors mention speed (infusion pump) and position (vaporizer) control, however no specific information are disclosed. Method limited to the control of a unique anesthetic agent.
Schwilden et al., 1985–1995 [15] [16] [71] [72]	Median Edge Frequency	Methohexital Propofol Alfentanil Isoflurane	Model-Based Adaptive Control Adaptation was done if the system output was diverging too far from its reference	13 volunteers (22-29 yr ; 44-85 kg) 11 volunteers (24-31 yr ; 54-87 kg) 11 patients 25 female patients (31-47 yr), ASA I or II	Results on volunteers have shown that a constant excitation is necessary the guarantee the reliability of the feedback quantity (otherwise the volunteers were drifting from a drug-induced unconsciousness into a natural sleep). This technique works also for opioids. The controlled drug was used as the only anesthetic agent during the maintenance phase.
Kenny et al., 1990–1995 [73] [74] [75]	Auditory Evoked Potentials	Propofol	Outer PI controller setting the reference to an inner TCI device.	27 patients	The authors recommended feedback control of anesthesia as a research tool to better identify pharmacodynamic models and the interaction between drugs.
Roy et al., 1995–2000 [76] [37]	Auditory Evoked Potentials	Halothane Propofol	Fuzzy rule-based control system controlling either the vaporizer or giving a reference to a TCI device	10 sessions conducted on 6 mongrel dogs with tail clamping stimulation 9 sessions conducted on 5 mongrel dogs	These papers emphasize mostly the hypnosis index derived from midlatency auditory potentials using wavelet analysis. Due to the extensive averaging needed, a value quantifying the level of hypnosis was calculated every 3 minutes.
Gentilini et al., 1995–2000 [57] [58] [77] [78] [79]	Mean Arterial Pressure Bispectral Index	Isoflurane	Model Predictive Control Cascade Internal Model Control. An inner loop controls the end-tidal concentration. The reference of the inner loop is set by an outer loop that regulates BIS variations	20 patients 40 patients (20-65 yr)	The control of inhalational gas such as isoflurane has the advantage that the drug plasma concentration is closely related to the end-tidal expired gas concentration which is readily available. This is a clear advantage over intravenous agents for which measurement of drug concentration is impractical. The authors have shown that isoflurane can both control the mean arterial blood pressure (MAP - sensitive to noxious stimuli) and the BIS (sensitive to the hypnotic level). The authors proposed to investigate a SIMO controller where isoflurane would be used to control both the MAP and the BIS
Struys et al., 2001 [55]	Bispectral Index	Propofol	A lookup table (Hill model) acquired during induction serves to calculate the required effect site concentration changes. A TCI device tracks these changes.	10 female patients (12-60 yr)	A continuous infusion of remifentanil was started 2 min before induction, thus the necessity to acquire a Hill curve that models propofol effect on the BIS with remifentanil acting as a bias. The results clearly indicate that the closed loop control of propofol significantly reduces recovery time as compared to the standard anesthesia practice. However, this benefit could only be the result of titrating the drug according to the BIS.
Absalom et al., 2002 [56]	Bispectral Index	Propofol	Outer PI controller setting the reference to a TCI device. There is an additional constraint limiting the maximum change of the infusion rate	10 patients (67 yr ±11 ; 79 kg ±11)	The authors present a comprehensive control algorithm based on a PI control structure. The way they calculated the gains and the time constant of the controller is not clear. 3 patients out of 10 presented severe oscillations where the BIS value was clearly leading the target plasma concentration, which is a clear sign of the instability of the outer PI controller.

TABLE I

Prior art: a literature survey