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Critically Safe General Anaesthesia in Closed Loop: Availability and Challenges

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Abstract: This paper provides an up-to-date review of intersecting know-how in engineering, medical and computer science frameworks. The text interweaves available measures, models, controls and technology for drug delivery systems in general anesthesia. The three main actors, equally important, along with their role in overall performance are presented and analyzed from a global perspective. The availability of patient information for personalized healthcare is systematically analyzed and the possibility to integrate this hybrid information sources into personalized patient models are critically sought. Finally, an important role is given to the accurate, crisp and real-time information availability in medical devices. Modular integration of new items is of paramount importance in terms of space, computational burden and number of training hours.

Keywords: closed loops, device, biomedical control systems, safety analysis, mathematical models, medical applications.

1. INTRODUCTION

Anaesthetic action at sub-cellular and cellular levels, and in neuronal networks within the brain and the spinal cord, contribute to a clinical state of unresponsiveness and unconsciousness that clinically represents *anaesthesia* (Schuttler and Schwilden, 2008). It is composed of numerous components of which sedation/hypnosis, antinociception, and altered autonomous reactivity are some of the prominent features. From the patient's viewpoint, the crucial effects of general anaesthesia are absence of consciousness and absence of pain. This translates into particular qualities of both general anaesthesia and anaesthetics:

1) sedation and reduction of voluntary responsiveness (hypnosis) – mental blockade;
2) analgesia / antinociception – sensory blockade;
3) motoric blockade to avoid movement to provide optimal surgical conditions (neuromuscular blockade);
4) autonomic blockade and stress shielding by blocking neurovegetative and cardio circulatory responses.

Items 3) and 4) are commonly monitored in clinical practice. Items 1) and 2) are difficult to separate and quantify and the remainder will focus on these two components. During *awake state*, the level of sedation and analgesia can be assessed by clinical evaluation. During *general anaesthesia*, with loss of response to stimuli, no parameter reliably indicates "deepening" or "lightening" of hypnosis or analgesia. Only unspecific surrogate parameters such as heart rate, blood pressure, sweating, tearing, etc, may indirectly indicate changes of the anaesthetic level.

In daily clinical practice of general anaesthesia, the goal is an individually tailored dosing of drugs, resulting in the 'optimal' anaesthetic level that is neither too light nor too deep. Under-dosage of anaesthetics leads to conscious perception or even awareness (conscious perception with explicit memory) during anaesthesia. As large multi-centre studies have shown in Scandinavia and United States, the incidence of this event is between 0.1% and 0.2% in an average population (Sandin et al, 2000; Sebel et al, 2004). This implies the risk of clinical consequences, e.g. pain flashbacks (Salomons et al, 2004). It is important to know that by the time of discharge from the hospital, patients may report that they are not suffering from any consequences of the awareness and yet experience consequences after a symptom-free interval. This latency has been reported on patients of the Scandinavian multi-centre study (Lemmarken et al, 2002).

Besides efforts to optimize anaesthesia to shield the patient from stress and consequences of surgery, cost saving and issues of economy may be an issue for dosing strategies (Song et al 1998; White et al 2004). Management of anaesthesia aimed at early recovery of the patient has been addressed as so-called 'fast track anaesthesia', which nevertheless comprises much more than optimized dosing of anaesthetic drugs. Therefore, knowledge of the pharmacokinetic and pharmacodynamic properties of anaesthetic drugs is imperative (Glass, 1998).

This paper provides an overview of the available measures and tools for obtaining a complex framework for optimal drug dosing system of depth of anaesthesia (DOA).

2. ELEMENTS OF A DOA PLATFORM

2.1 Measuring Drug Effects

For peri-operative management of general anaesthesia techniques, the following main drug classes are widely used

in clinical practice and of particular interest: hypnotic (propofol, etomidate, barbiturates, ketamine, and inhaled anaesthetic agents), analgesic, and narcotic drugs (morphine, opioids), sometimes supplemented by benzodiazepines and α_2 agonists.

Clinical mental blockade is relatively well assessed. This can be done using either spectral-based methods, such as the Bispectral Index (BIS) (Aspect Medical Systems, Norwood, MA, USA), or using evoked potentials (e.g. auditory) (Mortier et al, 1998; Dumont and Ansermino, 2013; Absalom et al, 2009). These indices do not directly measure unconsciousness or unresponsiveness. However, trough extensive clinical validation it is clear that these measures are predictive or likelihood of response, provided that the anaesthetic state has been induced with the drugs used to calibrate the electrophysiological measure (Liu et al 2011; Struys et al, 1998).

Sedation is assessed using OAA/S (observers assessment of alertness/sedation scale), which is a standardized questionnaire based on a combination of observations in the resting patient and responses to verbal commands with increasing intensity (Kress et al, 2002).

Adequacy of *analgesia* and antinociception during anaesthesia and surgery is complex. With insufficient analgesia/antinociception, noxious stimuli are perceived and lead to a subcortical stress response. With adequate analgesia/antinociception, the perception of a noxious stimulus and the subcortical stress response are blocked. With increasing stimulus intensity, a higher dose of analgesic drugs is required to reach adequate analgesia/antinociception. In addition, the level of analgesia is dependent on the degree of mental blockade (i.e. the hypnotic component of anaesthesia). Assessment of adequacy of antinociception is characteristically a *stimulus-response* type of measurement.

Similar to the development of a combined EEG (auditory evoked potentials) index, an index composed from different parameters may indicate the level of antinociception (Luginbuhl et al, 2010). During the development of such an index, one must control the input (noxious stimuli) and the level of antinociception (level of analgesic drug) in individuals and measure the response to this stimulus. However, difficulty arises from inter—individual variability.

2.2 Patient Models

Clinical practice of drug delivery systems and protocols in DOA regulation is limited to TCI or target controlled infusion (open loop, no feedback information from patient used). Patient models which give an indication for suitable drug titration to the anaesthesiologist are still based on averaged population compartmental models (Absalom et al, 2009; Minto et al, 1997; Schnider et al, 1981; Schnider et al, 1998), schematically represented in Figure 1.

Compartmental models are augmented with an extra 'effect-site' compartment, to which corresponds an effect-site concentration (Ozcan et al 2012; Kress et al, 2002). The plasma is not the site where the drugs unfold their clinical effects. This is usually the brain, measured via EEG or evoked auditory potentials. Hence, the main effect at the brain (effect site) is delayed when compared to plasma peak concentration; this is represented by adding an extra compartment.

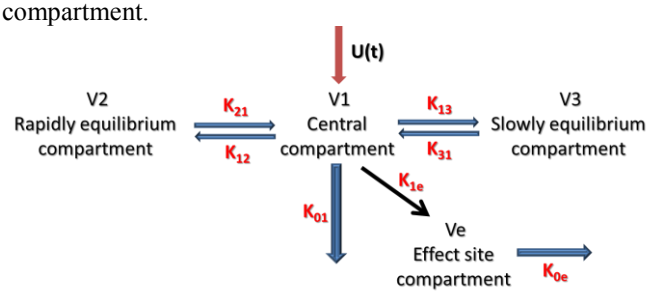

Fig. 1. The addition of an effect site to a three-compartment model refers to the fact that the anaesthetic effect takes place in the brain and not in the plasma. The effect site is calculated as with a negligible volume.

The effect site is connected to the central compartment by a first order process, where the constant k_{e0} is the rate constant for elimination of drug from the effect site. This coefficient has a large influence on the rate of rise and offset of drug effect, and the dose required to produce a certain drug effect. The volume of the site effect is neglected. The model in Figure 1 is represented by the following set of equations (Minto et al, 1997; Schnider et al, 1981; Schnider et al, 1998):

$$\begin{aligned}
\dot{q}_1(t) &= K_{21}q_2(t) + K_{31}q_3(t) - K_{12}q_1(t) - K_{01}q_1 + u(t) \\
\dot{q}_2(t) &= K_{12}q_1(t) - K_{21}q_2(t) \\
\dot{q}_3(t) &= K_{13}q_1(t) - K_{31}q_3(t) \\
\dot{q}_e(t) &= K_{1e}q_1(t) - K_{0e}q_e(t)
\end{aligned} \tag{1}$$

where: q denote the concentrations in the various compartment, U - dosing scheme as a function of time; K_{01} - rate constant reflecting all processes acting to irreversibly remove drug from the central compartment; K_{12}, K_{13}, K_{21}, K_{31}, K_{1e} - inter-compartmental rate constants [*mg/l*]; V_1 - volume of the central compartment [*l*], V_2 and V_3 - volume of the peripheral compartments [*l*] (respectively muscle and fat).

The drawback of these models is mainly the fact that *specificity* of the patient is lost and creates side-effects which either prolong patient's hospitalisation or treatment, either put his life and well-being in peril. In practice, drug titration in anaesthesia is still an *art* rather than a science, given the numerous unknown specific dynamics of the patient's response to drug effects and thus lacks a personalised healthcare approach. Due to this situation, a great responsibility lies upon the anaesthesiologist's shoulders.

Efforts to relieve this responsibility and aid anaesthesiologists in their critical and crucial decisions, and to avoid life-threatening situations, have led to the development of closed loop drug dosing control algorithms, including thus feedback information from patient's current state. Most of these control schemes are based still on population models, but they are still providing improved performance over open loop titration protocols (Mortier et al, 1998).

The state-of-the-art, however, offers possibilities to adapt these averaged population models to the specific patient undergoing DOA regulation, with successful (although limited) clinical trials over the landscape of European clinical research centres. Patient models, such as described by (1), which take into account physiological aspects, drug pharmacokinetics and drug pharmacodynamics

have been successfully employed with control algorithms for better drug dosing, avoiding over- and under- dosing of the patient.

An *alternative* approach to physiologic and compartmental modelling is to use parsimonious models which lose their link to physiology, but have the advantage of less number of parameters for adaptation to the specific patient. There are several types of such models; parsimonious models of the form:

$$G(s) = \frac{b_0 + b_1 s + b_2 s + ... b_{n_b} s^{n_b}}{a_1 s + a_2 s + ... a_{n_a} s^{n_a}} \quad (2)$$

with integer-order n_a and n_b have been published in (Lemos et al, 2014; Rocha et al, 2014).

The *emerging non-classical concepts of fractional derivatives and fractional functions* (in time domain) and fractional order impedance models (in frequency domain) have made the core of the original research performed in the last decade by few research groups (Ionescu 2012; Dokomuetzidis et al, 2010; Popovic et al, 2010, 2011). However, research is still needed to prove that these kind of models can improve the perception of today's patient response to drug interactions.

If one considers the patient as a black-box system into which an anaesthetic drug (input) is administered, and some output is determined as the therapeutic surrogate end-point, one may distinguish between the following four models of drug dosing:

1. input is independent of all previous outputs and all previous inputs: naïve dosing;
2. input is independent of all outputs, but may depend on previous inputs: TCI;
3. input is independent of all previous inputs but may depend on previous outputs: naïve feedback (e.g. PID control);
4. inputs depend on previous inputs and previous outputs: model based closed loop control (adaptive);
5. input depends on past inputs and outputs, and predicted outputs: model based predictive control (possibly augmented with model adaptation).

2.3 Open loop and closed loop control

Integrated pharmacokinetic-pharmacodynamic (PK-PD) models have proved to be a useful mathematical framework to institute such drug delivery to patients. The theory of model-based interactive drug dosing on the basis of common PK-PD models is outlined and TCI is presented as a new anaesthetic dosing technique that has developed during the last two decades (Glen 1998). TCI has relevance at other biomedical control fields as well. For example, diabetes control, where the control target is to hold the patient's blood glucose level in a narrow range through insulin infusion or anti-angiogenic targeted cancer control, where the target is to decrease the volume of cancer with anti-angiogenic drug (Szalay et al, (2014), Kovacs et al, (2014)). Whereas TCI presents an open-loop dosing strategy (the past output does not influence the future input), current research deals with the model based adaptive closed-loop administration of anaesthetics. In these systems the past output is used to adapt and individualize the initial PK-PD model to the patients and thus has an influence on future drug dosing which is based on the adapted model.

Anaesthesia regarded from the aspect of drug therapy has a number of particularities, as compared to other medical specialties; to these belong:

- duration of therapy is confined from a few minutes to a couple of hours and the onset of therapeutic effects such as loss of conscience or neuromuscular blockade should occur within seconds to very few minutes;
- the effects and side-effects of the drugs used are lethal if special measures, e.g. artificial ventilation, are not taken;
- the conscious response of the patient to drug delivery is not available and cannot be used to guide drug therapy.

As a consequence of these particularities, it appears natural that a dosing strategy which requires a time-consuming careful titration of drug dose to drug effect is obsolete; instead, short-acting drugs with a quick onset of action and a high degree of predictability are required. Predictability in this context means that the laws governing the time course of drug action after the delivery of drug into the central circulation of the human body are reliable and have a reasonably limited inter-individual variability.

In the past three decades blood concentrations of intravenous anaesthetics served as targets which give rise to TCI (Glass et al, 1997) systems for the delivery of intravenous anaesthetics. Typical control systems consist of five parts (see Figure 2):

1) the patient as the system to be controlled;
2) the response, which is considered as a measurable representation of the process to be controlled;
3) a model of the input-output relationship;
4) an adapter which could be part of the model block;
5) a controller, linear of nonlinear.

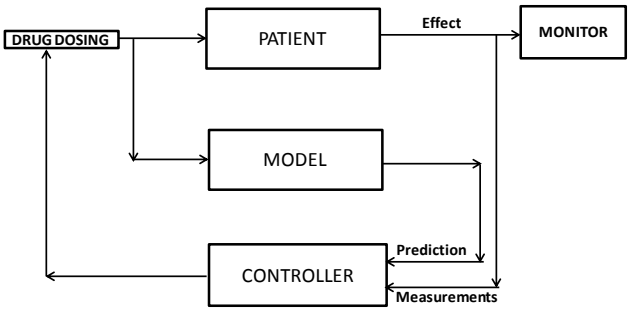

Fig.2. Block diagram of a model based (adaptive) closed loop system for automatic drug delivery.

For the development of an EEG-based feedback controlled administration of intravenous anaesthetics one can combine the PK-based TCI approach with target selection as determined from the PD (see patents of Struys and patents of Grosley). The relationship between concentration and the measured effect can be modelled according to a nonlinear Hill function (Schuttler and Schwilden, 2008) or to a piecewise affine Hill function (Ionescu et al, 2015). In the past few years, model-based feedback systems using Bispectral Index as the EEG parameter have been investigated in more detail with respect to performance and in comparison to 'standard clinical practice' (Mortier et al 1998). The conclusion was that feedback systems have the potential to be more practical, more effective, more

economical and more patient-friendly than traditional approaches in clinical research.

2.4 Safety

The primary concern in any computerized system in health care is safety. In human-supervised drug delivery regulation systems, ventilators, dialysis, etc, safety becomes an especially complex and multi-faceted matter. In addition to mechanical and electronic hardware, such computerized systems incorporate advanced software implementing signal processing and control algorithms that are based on mathematical models (Zhusubaliyev et al, 2015). Therefore, three groups of monitoring functions have to be in place ensuring system component integrity and covering hardware, software, and mathematical models, respectively.

The monitoring functionality has to incorporate fault detection, isolation, and accommodation. Furthermore, the overall system performance has to be monitored as a safeguard measure against systemic faults caused by malfunction in or irregular interplay between a number system blocks (subsystems). Measures have also to be taken to prevent unintended use of medical equipment as well as to provide guidance to medical personnel in their interaction with the system.

There are several aspects of safety in monitoring systems:

- fault detection;
- fault isolation;
- fault accommodation;
- software safety;
- mathematical patient model safety, and
- function monitoring.

Methods for detecting mechanical and electrical faults in system blocks fall into two groups targeting either drastic or incipient faults. Fault detection raises an alarm when a system component does not function properly. To indicate the reason for an alarm and pinpoint the failing component, fault isolation has to be used. Methods for fault isolation intrinsically exploit physical or analytical redundancy in the system. The necessity for an accurate model capturing the system dynamics both in normal and abnormal operation presents a major design challenge.

When the reason for the fault or location thereof is isolated, a suitable chain of actions has to be initiated in order to minimize the fault impact on the system function or enable graceful system degradation. In medical systems, safety protocols dictate system shutdown on a single detected fault, unless the system is mission critical, e.g. a mechanical ventilator without backup or a pacemaker. Transfer to manual mode or controlled system shutdown has to be handled with preserved patient safety notwithstanding faults and facilitated by the information provided by fault isolation algorithms.

Medical systems become increasingly software-intensive and implemented by means of embedded in medical devices and stand-alone programs. The problem of software safety becomes especially intricate with the arrival of parallel processors in medical applications as the complexity of programming rises significantly (Rosen and Medvedev, 2011).

Signal processing and control algorithms embedded in medical devices and systems are in most cases based on mathematical models. Stability and robustness of the closed loop control must be guaranteed at all times and patient safety ensures through active constraint sets. Backup loops to TCI or manual mode must be introduced such that risk is minimized with respect to patient's safety and well-being. Particular attention needs to be given to the presence of time delays (Ionescu et al, 2011) and possible compensating schemes introduced (Pop et al, 2012).

3. INTEGRATION INTO A CYBER-PHYSICAL PLATFORM

Some of the main characteristics of a Decision Support System (DSS) are summarized below:

1. it has to be the framework for all subsystems, this will be brought together the subparts
2. it collects all necessary and/or available data from heterogeneous sources
3. it contains different use-cases for all user types
4. it is appropriate for defining patient models
5. it is able to realize different control strategies based on the models
6. it has expedient, ergonomic and suitable Graphical User Interface (GUI)
7. it can be used on different platforms
8. it should be module based
9. it supports operation and therapy as well.

Many DSS exists, focused to larger or specialized areas (e.g. Kozlovszky et al, 2014). Because usually the resources are limited, DSS should be a module-based, specialized system, but with easy expandability. Communication between the different subparts and external system is critical, as one needs to collect a lot of data from several sources; it is necessary communicating with medical actuators (drug delivery systems, etc.); the suggested action is need to be displayed, stored, etc.

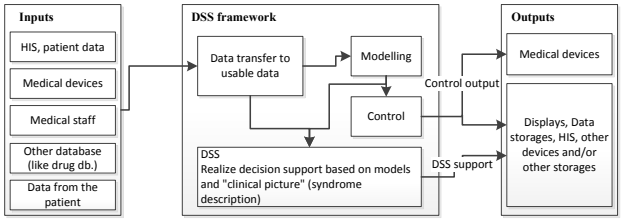

Fig. 3.Simplest abstraction of the system as whole

As a whole, the basic requirements of the DSS from Figure 3 is to have a set of inputs, carefully evaluated and processed, in order to provide some outputs with clinical relevance. Possible input data sources can be the following items.

Hospital Information System (HIS). In practice, every medical provider has some kind of information system, where data are available from the patient. Because the environment of the DSS is typically a hospital, a suitable solution is enabled if the system can directly be connected with a given HIS. That is not a trivial task due to the numerous and not homogenized HISs, which are used in different hospitals across Europe. Usually, the HISs contain a lot of data from each patients (in electronic form under the name of Electronic

Patient Database – EPD), but in most of the cases, this data are not well structured or if structured, then it may not be in a suitable form that can be used directly (scanned document, pictures, medical records, etc.).

Interaction Between Sub-Systems and Inter-connected Devices. Data needs to be collected from a manifold of monitoring and life support devices. The main problem is the interface variation between these devices – the medical providers are using different medical devices from different manufacturers, but if the devices came from the same manufacturers it can occur a difference between them (e.g. diversification, newer series, etc.).

The patient. Feedback information from the patient is necessary in the therapy and in the operation, as well. Obviously, the possible data feedback during operation is highly reduced – in this case the feedback from the current state of the patient comes from diagnostic devices. At therapy, to assess the actual state of the patient, we have to accumulate the direct and indirect state indicators. Direct state indicators are the opinion of the patient verbally and automatic (even through a potentiometer like solution, or something similar). Indirect state indicators are the monitoring devices (even 24h monitoring, implanted to the bed, or else). These data are needed to the modeling and control, and DSS parts, too.

The nursing staff. Most of data from the staff is mirroring the HIS, but there are subjective data or not recorded data, which are maybe important, too. Expertise and know-how levels of the staff play a major role as well and variations in handling protocol of critical or life-threatening situations may occur.

The information which is produced by the DSS need to transform to usable data format for the users. These users can be medical devices (actuators, drug delivery systems, etc.) that get this information as a control input. With these, the closed-loop control for DOA regulation is realizable through the DSS framework (see Figure 4).

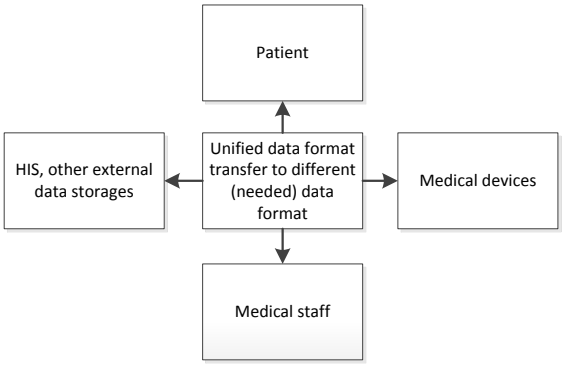

Fig.4. Interacting sub-systems of DSS

In the context of personalized healthcare (personalized patient models), these platforms and the patient models within these platforms should be customizable (Soltesz et al 2013). There are two ways for that: manually and automated methods. The manual customizing methods mean that an environment exists where the bulk of the tuning is made by algorithms and the remaining "fine tuning" part is made by the medical staff. This is the current clinical practice. On the other hand, to achieve an automated way to customize patient healthcare, one has to introduce the concept of model adaptation and control auto-tuning methods. The certification of these tools needs to be done also in an automated way, as part of a system's *calibration to the patient specificity*.

The possible outputs from control subpart are output(s) to the DSS subsystem and output(s) to medical actuators. The latter is obvious – through this connection, the closed-loop control can be realized, as sketched in Figure 5. The control subpart is able to improve the efficiency of the DSS.

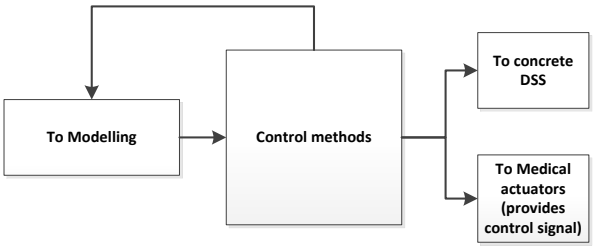

Fig.5. Interaction of DSS in the context of closed loop control

4. CHALLENGES

In this section we present some of the challenges associated with the development of personalised healthcare in the context of drug delivery systems in general, and DOA regulation in special. As a general remark to the current state of art of DOA regulation, one should be aware of the fact that the development of systems which are able and are safe to work under daily routine conditions is several orders or magnitude more difficult than developing a research tool.

The transition from state of the art to clinical practice is that we lack the basic requirement in assessing sensorial blockade; namely, the development of a reliable clinical reference score that remains valid once consciousness is lost.

Apart from feedback information availability through sensors, one also needs to tackle the hybrid nature of the input sources of the DSS and their transferability to directly usable data.

If closed loops are superior to manual control, one should expect a widespread use of such devices, which is obviously not the case. The reason is that this technology is not fully developed. So far, all the applications in clinical anaesthesia have been used in a research environment, and it has been shown that feedback systems can be very powerful research tools (Ionescu et al, 2011; Ionescu et al 2014).

It still remains to be shown that closed loop systems will safely operate under common daily clinical conditions and provide better control of drug administration. To this end, additional research and development is needed, especially in two areas:

1) sensor technology;
2) artefact detection and elimination.

The use of monitors in anaesthesia seems to indicate that redundancy could be a successful approach to tackle this problem because it brings focus to multi-input multi-output control (Rocha et al, 2014; Soltesz et al 2013, Ionescu et al 2014).

Advanced control strategies, such as gain adaptation techniques (Nino et al, 2009) or nonlinear control techniques (Nascu et al, 2015; Syafiie et al, 2009) could be introduced as well to improve the overall performance and stability.

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