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Automated Drug Delivery in Anesthesia

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ABSTRACT
Automated drug delivery by a closed-loop system has been proposed to optimize drug delivery during anesthesia and sedation. A closed-loop system can make decisions independently and attempt to achieve and maintain certain goals. This review describes milestones and recent developments in automated drug delivery systems applicable during sedation, anesthesia, and postoperative analgesia. The main goals of general anesthesia are proper hypnosis, analgesia, and preservation of vital functions. Neuromuscular blockade is essential for many surgical procedures. Furthermore, patient safety and cost savings through minimizing drug consumption and shortening postoperative recovery are major topics and motivators for automation efforts in anesthesia. Since the early 1980s, engineers and medical professionals have worked together to develop closed-loop drug delivery systems. This work, without claiming to be complete, merely provides a brief overview of recent developments in automation of drug delivery systems, and expresses a much more vision. The control system, the so-called Rostock Assist System for Anesthesia Control (RAN), will be equipped with the option of automatically controlling four different drugs. Currently, multiple-input multipleoutput (MIMO) control of hypnotic depth and neuromuscular blockade and closed-loop control of deep hypotension are being realized. A pilot study to regulate analgesia is currently underway. This paper includes some general caveats and a MIMO system designed to control hypnotic depth and neuromuscular blockade. keyword:Targeted injection Closed-loop Propofol Bayesian optimization Automated drug delivery PID

I. INTRODUCTIONS
Changes in techniques and patient populations make it more challenging than ever to manage anesthesia in a fast, simple and safe way. A wide spectrum of pharmacological M. M. Neckebroek Department of Anesthesia, University Hospital Ghent, De Pintelaan 185, 9000 Ghent, Belgium. be T. De Smet Demed Medical Engineering, Hollebeek 145, 9140 Temse, Belgium.be M. M. R.

F. Struys (&) Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands . nl M. M. R. F. Struys Ghent University, Ghent, Belgium actions (analgesia, hypnosis, and suppression of somatic and autonomic responses to noxious stimuli) are needed to control the general anesthetic state In clinical practice anesthesiologist have to observe and control a huge amount of hemodynamic and respiratory variables as well as clinical signs of adequate hypnosis and analgesia. In neuro-, thoracic- and abdominal surgery a continuous neuromuscular block is needed to guarantee optimal surgical conditions [1]. During general anesthesia, opiates are classically applied to manage the nociception–antinoception balance, and short acting hypnotics are widely used to titrate the hypnotic component of anesthesia. The ultimate goal when administering a particular dose of an anesthetic or analgesic drug is to obtain the desired clinical effect, for which a specific therapeutic concentration of the drug at the site of action (=the receptor) is required. At the same moment, the clinician wants to avoid side effects in order to reach the highest standards of care. In the world of control engineering, dealing with the behavior of dynamic systems, closed-loop control can be

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defined as the management of single- or multipleoutput variables of a system following a specific target value, whereby a controller adapts the system's inputs to reach and maintain a desired effect on the output. The goal of a closed-loop controller is to calculate solutions for an accurate corrective action from the controller that result in system stability, that is, the system will hold the set point and not oscillate around in [2]. Extrapolated to the world of anesthesia, this means that any action to maintain a specific pharmacological effect can be called a closed-loop control. Even a manual titration of drug infusion by a clinician is a closed-loop action as the clinician continuously monitors and adapts his/her actions. However, the7j clinician serves as the ''human controller'' in the loop, and as a consequence the control actions are intermittent and irregular in time [3•]. Computer-based closed-loop administration requires various system components : (1) a controlled variable representative for the targeted therapeutic effect; (2) a clinically relevant set- point or target value for this variable; (3) a control actuator, which is, in this case, the infusion M.
M. Neckebroek Department of Anesthesia, University Hospital Ghent, De Pintelaan 185, 9000 Ghent, Belgium e-mail: martine.neckebroek@ugent.be T. De Smet Demed Medical Engineering, Hollebeek 145, 9140 Temse, Belgium e-mail: tds@demed.be M. M. R. F. Struys (&) Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands email: m.m.r.f.struys@umcg.nl M. M. R. F. Struys Ghent University, Ghent, Belgium 123 Curr Anesthesiol Rep (2013) 3:18–26 DOI 10.1007/s40140-012- 0004-3 pump driving the drug; A system, in this case a patient; (5) an accurate, stable control algorithm [4]. Various closed-loop systems exist to control various steps in the doseresponse relationship. When a system is able to control a specific set dose or drug concentration, it can be called a pharmacokinetic closed-loop controller. When a specific therapeutic effect is targeted, the control system is defined as a pharmacodynamic closed-loop system. 4

PHARMACOKINETIC CLOSED-LOOP SYSTEMS IN ANESTHESIA

Expired concentration of various drugs can be measured continuously. For the inhaled anesthetics such as desflurane, sevoflurane, and isoflurane, this can be done clinically using the spectrometric gas analyzers available in most of the anesthesia monitors. Using these inhaled anesthetic concentrations, a closedloop system can be applied targeting a specific inspired or end-tidal concentration. Over the last decades, various experimental control systems were developed 5, 6]. More recently, a commercial closed-circuit anesthesia ventilator (Zeus, Dra¨ger Medical, Lu¨beck, Germany) was released. This machine is able to target the end-tidal concentrations of inhaled anesthetics and to control the fresh gas flow using closed-loop technology [7]. Recently, experimental devices measuring exhaled concentration from intravenously given propofol have been tested using proton transfer mass spectrometry and headspace solid-phase microextraction coupled with gas chromatography-mass spectrometry (HS-SPME-GC-MS)[8] or ion mobility spectrometry coupled to a multicapillary column for pre-separation (MCC-IMS). Grossherr et al.[9] used gas chromatography mass spectrometry to measure exhaled propofol. Until today, propofol exhaled concentration measures are still experimental and no closedloop systems have been developed using this concentration as the controlled variable.

PHARMACOKINETIC-DYNAMIC CLOSED-LOOP SYSTEMS

The Controlled Variable The accuracy of closed-loop controlled drug administration strongly depends on the robustness and reliability of the controlled variable. Various drug actions can be measured directly using physiological measures. Examples are heart rate, respiration, blood pressure, and neuromuscular blockade. Various research groups have used direct measures to steer the feedback from controlled administration of cardiovascular drugs, anesthetics and muscular blocking agents. Some of these systems, such as the IVAC Titrator (Carefusion, San Diego, CA, USA) controlling nitroprusside using blood pressure as controlled variable, had been commercially available in the past but were discontinued. In contrast to these direct measures, surrogate measures are required to observe the hypnotic component of anesthesia or the balance between nociception and antinociception. However, they have to be interpreted with caution as a full correlation with all levels of drug effect might be missing. Various surrogate measures have been studied to observe hypnotic drug effects. Both the spontaneous and evoked electro-encephalogram (EEG) have been proven to accurately measure cerebral hypnotic drug effects and be good candidate controlled variables closed-loop of hypnosis. Early closed-loop systems used computerized EEG derivatives

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like spectral edge frequency (SEF) and median frequency (MEF) [10]. More recently, the bispectral index (BIS, Covidien, Boulder, CO, USA) has been used as controlled variable in multiple studies. BIS has been designed using multivariate statistical analysis, to combine multiple EEG features, including higher-order spectra and phase correlations between spectra into a more accurate indicator. Aside from BIS, State and Response Entropy (M-entropy, GE Healthcare, Helsinki, Finland), two spectral entropy parameters based on the irregularity in the EEG have been used recently to measure hypnotic drug effect 6 during closed-loop administration[11–13•]. One research group has tested auditory evoked potentials, more specific the midlatency auditory evoked potential (MLAEP) as controlled variable for closed-loop control of propofol administration [14, 15]. One of the major challenges when using a surrogate measure is the delay in the system, which adds complexity to the controller. All currently available indices have different time lags to react to a change in the level of anesthesia. Pilge and coworkers compared the time lag in three commercially available computerized EEG systems by using an artificial EEG signal and found time variable delays between 14 and 155 s [16]. Closed-loop administration of analgesics have been challenging because controlling the balance between nociception and antinociception is a difficult task. Liu et al. [13•] have used EEG to co-administer propofol and opioids, however, the inclusion of a real ‘‘analgesia index’’ in closedloop is still lacking. Using the difference between response (RE) and state (SE) entropy derived from the EEG as a measure of frontal electromyographic (FEMG) activity, Mathews and coworkers found that remifentanil may be delivered using an algorithm that maintains the difference between RE and SE between the upper and lower boundary condition [17], however, this has not been incorporated in a closed-loop system. More recently, the same authors found that the Composite Variability Index (CVI), based on the variability in BIS and FEMG activity, might be useful to predict movement during anesthesia, which can be controlled by administering

THE TARGET VALUE

The target value or set-point is the value set by the clinician and will be approached as closely as possible during the maintenance of anesthesia. A clinically adequate individual target is essential for the accuracy of the closedloop system. Two types of set-points can be used: (1) set-points that are based on population mean data, or (2) individual data measured at the start or just before the control period. The latter type could be expected to more closely correspond to the clinical needs during the course of a surgical procedure[19]. Control Methods Multiple control methods have been used to guide closedloop anesthesia. Although on–off control was used in the early days, severe oscillation due to the complexity of drug behavior have limited thisapproach[20–24]. ProportionalIntegral-Derivative (PID) control has also been used in various anesthesia-related closed-loop applications. A PID controller is based on a straightforward mathematical derivative of the observed error, and can be written as: dR=dt ¼ KP dð Þ err =dt þ err=KI þ KD d2 ð Þ err

=d2 t ðformula 1Þ with err, being the error between the target and the observed value, causing a response R in the actuator. The constants KP, KI, KD are tuned by calculations from models of the system, by computer simulations, or derived from trials using tuning rules [25]. PID controllers have been applied under well-controlled situation after fine-tuning of the constants [26–29]. However, the use of a general PID controller to control the complex dose–response relationship when administering drugs (with R being the administration rate), could be slow in establishing control and may cause oscillations. The complexity of the dose-response relationship can be decreased by implementing knowledge of the pharmacokinetic-dynamic behavior of the drug. Incorporating pharmacokinetic-dynamic models will enable a controller to use a specific plasma or effect-site concentration as R (see formula 1) instead of a dosing rate. The use of plasma or effect-site targeted drug administration is well understood and will lower the order of complexity of the resulting system [30]. Nowadays, the use of modern powerful microprocessors may allow better control through the incorporation of more sophisticated models describing the dose– response relationship, or by reverting to other control algorithms like MPC or fuzzy logic 31, 32]. Closed-loop control might benefit from adaptive finetuning. 8 Various theoretical approaches can be used to adapt the control parameters toward the behavior characteristics of a specific individual. Examples are state estimation, mixed-effects pharmacokinetic or dynamic modeling using Bayesian estimation [33•, 34], Kalman filtering [35], fuzzy logic [36] or other engineering techniques such as neural network applications[37] and reinforced learning [38, 39]. Bayesian

optimization, as proposed by Sheiner and coworkers [40], individualizes the pharmacodynamic relationship by combining individual information with the knowledge of an a priori probability density function containing the statistical properties of the parameter to be estimated[41]. The Bayesian method starts from a standard, population-based response model providing the prior distribution of parameter values. These values are adjusted to reflect the patient's own parameters over time, based on the observed response of the individual patient under varying circumstances[42]. The Kalman filter will apply a recursive method to calculate numbers for a given doseresponse relationship for the specific patient, for example to individualize the constant for plasma-effect site equilibration [43, 44]. Fuzzy logic control is based on fuzzy set theory as proposed by Zadeh [45] in the sixties. An approach of model adaptation based on fuzzy logic was proposed by Kern and coworkers [46]. Recently, Moore and Doufas used reinforcement learning to control propofol closed-loop administration in a simulated environment. Reinforcement learning (RL) is an intelligent control method with an excellent record of success in difficult robotic control tasks. This method is based on a mathematically structured framework for goal- directed decisionmaking and is suitable for biological applications that are characterized by an inherent time delay between control actions and effects [38, 39]. Examples of Closed-Loop Drug Administration Human-operated drug administration can be considered as a form of closed-loop control. Various patient-controlled drug administration 9 systems are available to deliver individualized dosages of analgesics and hypnotics. This technology, called patient controlled analgesia (PCA) or patientcontrolled sedation (PCS) systems, offers the possibility to set a continuous background infusion and to allow patients to administer themselves additional top-up dosages. PCA without background infusion is also used. Postoperative PCA usage has been described for analgesics such as morphine, piritramide, fantanyl, tramadol, and others [47–51]. In a systematic review, Walder and colleagues showed that the some evidence exists that in the postoperative pain setting, PCA with opioids, compared with conventional opioid treatment, improves analgesia and decreases the risk of pulmonary complications, and that patients prefer this option [52]. The development of advanced drug delivery devices that offer lockout times and total amount of drug delivery per time is required. Strict hospital guidelines are required avoid drug overdose, causing potentially life-threatening side effects such as respiratory depression [53]. Recently, the feasibility of the use of intravenously delivered remifentanil during labor by PCA, under strict observation, has been demonstrated [54–59]. Large randomized controlled trials are required to prove that this technique can become an alternative for epidural analgesia during labor[60•]. PCS might offer comfort and anxiolysis during therapeutic procedures such as endoscopy. Various experimental devices for propofol PCS administration have been designed in the past[61–63], some of these even adding TCI technology into the system to optimize drug delivery[64–67]. Doufas and colleagues tested an automatic response test to optimize propofol administration for conscious sedation and showed that failure to respond to automated responsiveness monitoring precedes potentially serious adverse effects of sedation such as loss of responsiveness, and that the monitor was not susceptible to false-positive responses[68–70•]. An enlarged commercial version of this device, called Sedasys (Ethicon EndoSurgery, Cincinnati, OH, USA) has been tested in two studies. 10 The system incorporates the automated responsiveness monitoring and in-built capnography and pulse oximetry. If responses to stimuli are inadequate, the increase in infusion rate is limited; whereas if apnea or hemoglobin oxygen desaturation is detected, then the infusion is stopped and additional oxygen administered. After a successful feasibility study[71], the system was then used in a large randomized study of sedation during upper gastrointestinal endoscopy and colonoscopy, and found to be associated with a reduced incidence of adverse events compared with standard care (5.8 vs 8.7 % respectively) [72•]. When feeding a continuously measured drug effect back to the drug delivery device, fully automated drug delivery will be enabled. The clinician has only to set a specific target value to be reached and maintained. Early perioperative closed-loop technology focussed on the administration of cardiovascular drugs and neuromuscular blocking agents. For example, Kenny and coworkers [73] successfully evaluated closed-loop control of arterial pressure using a mixture of trimetaphan camsylate and sodium nitroprusside during controlled hypotensive anesthesia for local resections of intraocular melanoma. In the 1980s–1990s, various researchers tested the accuracy of closed- loop controlled administration of atracurium [74] and vecuronium [75]. Due to the commercialisation of the reversal drug

suggamadex, interest in closed-loop administration of muscle relaxants has declined. Early developed closed-loop system used hemodynamic alterationsto guide hypnotic drug delivery, due to a lack of availability of reliable cerebral drug effect monitors, such as EEG [21, 22, 31]. The commercialisation of more accurate cerebral effect measures enabled the development of EEG based closed-loop delivery of hypnotic-anesthetic drugs. Schwilden and Schu¨ttler pioneered closed-loop administration of methohexital [76], propofol [77] and even alfentanil [78] using the EEG median frequency as controlled variable and an adaptive controller based on pharmacological principles, whereby adaptation in the pharmacokinetic part was applied. Kenny 11 and coworkers developed a proportional-integral (PI) based closed-loop system for propofol administration using a mid-latency evoked potential derived index (AEPindex) as the controlled variable. The input variable was the predicted plasma concentration of propofol. As explained earlier in this chapter, concepts of TCI were applied to decrease the complexity of the PI controller. Accurate control was observed in most of the patients [14]. Most of the recent developed hypnotic closed-loop systems are guided by the EEG-derived bispectral index or BIS. Sakai and colleagues used an early version of the BIS and concluded that their closed-loop system provided intraoperative hemodynamic stability and a prompt recovery from sedative–hypnotic effects of propofol [79]. Absalom and Kenny proposed propofol closed- loop delivery using BIS and PID control of a plasma controlled TCI system and revealed acceptable control during major orthopedic surgery [30] and during sedation[80]. Although these researchers improved the performance of their control system by implementing more advanced effect-site targeted TCI, they also concluded that the PID controller might still face some stability problems. A similar BISguided propofol closed-loop system using a control system described as a proportional-derivative (PD) control to steer a specific effect-site concentration was developed by Liu and coworkers. Their system was tested during anesthesia and resulted in lower propofol consumption, longer induction time but with better hemodynamic stability, less excessive anesthetic levels (BIS \40), similar hemodynamic stability and faster recovery [81, 82]. More recently, Liu tested a more advanced version of their BISguided system, now claiming full PID control, for closed-loop coadministration of both propofol and remifentanil. On top of the PID controller, the authors describe a rule-based algorithm that determines when to change the propofol or remifentanil targets. This system showed a better overall performance compared to manual administration in a multicenter study [83]. A similar approach was used with an alternative EEG- 12 derived index, spectral entropy [13•]. Recently, Liu fully explained his control system in a response to a letter to the editor of Anesthesiology. In this letter, Looke criticized the approach by Liu and coworkers by stating that the system should not be described as a PID Curr Anesthesiol Rep (2013) 3:18–26 21 123 controller, but as an empirically derived expert system controller. This author stressed on the importance of using a multidisciplinary team approach, including both medical and control engineering professionals when developing closed-loop systems, and stressed also on the application of simulation studies before entering into clinical practice. In their reply, Liu and coworkers revealed in great detail the structure of their algorithm and PID properties are certainly recognized. They also debated on the utility of simulation studies during closedloop development [84]. As said previously, automated drug delivery could benefit from the implementation of principles of pharmacokinetics and dynamics in the control algorithm. A BIS- guided, patient-individualized, model-based adaptive control system was developed and tested by Struys and De Smet during sedation and general anesthesia [85, 86]. The controller is based on a pharmacodynamic model represented by a sigmoidal Emax model. Initially, the initial patient- specific pharmacodynamic profile is calculated automatically during induction by correlating all predicted effect-site concentrations with the corresponding BIS value. During closed-loop control, the controller minimizes the difference between measured and desired effect by using the pharmacodynamic model [86]. The authors compared this closed-loop controlled administration of propofol versus standard practice controlled administration and concluded that closed-loop control was clinically acceptable. In an accompanying editorial, Glass and Rampil [87] questioned whether the controller could become clinically acceptable outside the study population, because all subsequent adjustments were based on a static pharmacodynamic curve and only BIS of 50 was targeted in combination with continuous infusion of propofol or spinal anesthesia. 13 As it might be considered unethical to stress the controller under extreme conditions outside the ranges of good clinical practice, a simulation study was undertaken and proved that even under extreme conditions, the model-based controllerexhibited no behaviour

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problems and performed better than a previously published PID controlled closed-loop system [88]. As the original controller assumed a drug-free patient and used a fixed pharmacodynamic curve individualized during induction, De Smet and Struys included Bayesian optimization (as explained earlier in this article) into the original modelbased controller to overcome these shortcomings (Fig. 1). They estimated the optimal modelling weights for this Bayesian-based BIS guided closed-loop system for propofol administration in a large simulation study, hereby stating that this system was safe enough to be introduced into clinical testing [34]. This accuracy and clinical feasibility was tested in a clinical study guiding propofol administration during anesthesia for ambulatory. Gynecological procedures. They demonstrated that this system outperformed her BIS-controlled, effect compartment-controlled propofol administration titrated by an anesthesiologist [33•]. For BIS- controlled isoflurane administration, a closedloop system was developed using a cascade controller first described by Gentilini et al. described [89, 90]. Recently, Moore and Doufas used an intelligent systems technique called 'reinforcement learning' to develop closed-loop systems that achieve optimal control in systems characterized by noise, nonlinearities, inherent time delays, and uncertainties. developed [38, 39]. This system has not been tested in a clinical setting. Most of the controllers above do not have a prediction period. Recently, Ionescu et al. described a model-based predictive control strategy that could form the basis for more advanced and future innovative engineering. In particular, these authors were able to demonstrate that updating adaptive models of patient pharmacodynamic profiles is possible. This allows us to detect significantly variable time delays in a patient's response to 14 drug infusion and the presence of artifacts within her ICU.

MEASUREMENT OF RELAXATION, HYPNOSIS AND ANALGESIA

a) Measurement of the muscle relaxation As discussed in section 1 a main concern of the anesthetist in the operating theatre is the monitoring and control of muscle relaxation. The evoked muscle response after supramaximal stimulation of its motoric nerve (e.g. ulnaris nerve - adductor pollicis muscle) can be registered by electromyography (EMG), mechanomyography (MMG) or acceleromyography (AMG). Most research groups working at the field of control the muscle relaxation prefer the EMG as integrated sum muscle potential measurement because it is easy to apply and less vulnerable to mechanical interferences then the other methods. An integrated complex neuromuscular monitoring system was developed in our group over the last years. The most common method to record the degree of muscle relaxation is based on measurement the muscle response after neurostimulation with a train-of-four (TOF) stimulation of a peripheral nerve. For the TOF-stimulation a series of four stimulations in an interval of 500ms, each stimulus 200 − 300µs long, is applied. A ”supramaximal” stimulation current is used to stimulate all fibers of the nerve (Silverman and Brull [1994]). The period of stimulation is limited to 10 − 12s because of the necessary physiological regeneration of the neuromuscular system. Since in a lot of applications the set point of 90% neuromuscular blockade is prescribed, stimulation patterns like train-of-four (TOF) are with regard to the twitch suppression not more effective than the T1-stimulation, with single twitches. By using the single-twitch stimulation mode (one twitch every 12 sec.) a control value T0 (T1%=T1/T0) is needed prior to the application of the muscle relaxant. The T1% value decreases after an initial bolus injection and the neuromuscular block increases. A typical setpoint can be adjusted at 90% neuromuscular blockade or T1=10%. In the current configuration we are using a T1-stimulated EMG + AMG registration of the neuromuscular blockade. 16 b) Measurement of the depth of hypnosis Anesthetists use different variables for estimating the depth of hypnosis, some of them like tearing and sweating are not measurable. However, the automation of the control of depth of hypnosis needs measurable outputs. Measuring depth of hypnosis is often discussed and no final answer can be given. A lot of research work concerning the measurement of the depth of hypnosis with different approaches was done over the last years (Bibian et al. [2003], Glass et al. [1997], Schwilden et al. [1989], Struys et al. [2002], Bruhn et al. [2000], Schneider et al. [2004], Tempe and Satyanarayana [2004]). Depth of hypnosis is expected to be reflected in the electroencephalogram (EEG). Different algorithms are known for estimation of residuals as indicator for the depth of hypnosis from the raw EEG. The main disadvantage of the EEG measurement is the variance with different anesthetic agents. Some algorithms are based on the calculated power spectrum of the EEG. The complexity of the raw EEG is decreasing with an increasing depth of hypnosis. The parameter of the spectral edge frequency 95% (SEF 95) determines the maximum

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frequency for 95% of the signal power. The correlation of the spectral edge frequencies is not closed, the use of the SEF as valid measurement for the depth of anesthesia is contentious (Widman et al. [2000]). An other index calculated from the EEG, the bispectral index (BIS), became very popular in the last years and has been validated in large studies. The precise algorithm is proprietary and has not been published. The algorithm combines the power spectrum and bispectrum with a burst suppression analysis. The BIS describes a complex EEG pattern within a simple variable. The BIS-Monitor is because of the powerful evaluation studies more accepted. The monitor calculates the level of hypnosis in a number from 0 − 100. 0 describes an isoelectrical EEG and 100 a wake patient. The developer of the algorithm advises a BIS-Index between 40 and 60 for general anesthesia. Another measurement procedure is the measurement of the response of the EEG on stimulation. The evoked potentials reflects the subjective clinical signs that anesthetists use routinely. The evoked potentials are an indicator for the responsiveness of the central nervous system (CNS). For measuring the depth of 17 hypnosis the BIS-Monitor A2000 with ”XP-software version” from ”Aspect medical systems” was implemented in the RAN. c) Measurement of the level of analgesia The main problem of measuring the analgesia level is the absence of parameters which describe the actual status. Therefore the notion of measuring the antinociceptive effect was used (Bibian et al. [2003]). A surgical trauma is usually accompanied with strong sympathetic and parasympathetic activity, like heart rate and blood pressure changes, sweating, etc. A combination, for example of changes in heart rate and changes in blood pressure is used in Nunes et al. [2005] to identify a inadequate analgesia level. The measurement of the Heart Rate Variability (HRV) is a rather new technique to quantify the analgesia and could be, in combination with a second parameter derived from vital function (Pomfrett [1999], Schubert et al. [2004]), a valid parameter for ananalgesia controller. In our research group we prefer the HRV measurement combined with blood pressure registration for analgesia quantification (Schubert et al. [2007]). A fuzzy-system for analgesia control was designed and is currently in the clinical test phase.

MODELING

For the controller design it’s much more favorable and desirable to use a model description. There are two ways to describe the effect of the drugs in the human body. The most popular way is to use a compartment model description. This idea will be discussed in more detail in the following chapter. Another way to describe the working mechanism of drugs in the human body are the physiological models. More details were presented in Stadler [2003] and Simanski et al. [2007]. The pharmacology is the science which is working in the field of drug distribution, - elimination and - effect. The most popular kind to model the drug distribution and elimination are pharmacikinetic-pharmacodynamic (PKPD) models. Pharmacokinetics means the dynamic process of drug distribution in the body and pharmacodynamics means the description of the effect of the drug on the body. Compartmental models are formulated on the basis of the minimal number of compartments that adequately fits observed data. Compartmental models are subdivided into simple, catenary and mamillary models, see Tucker [1990]. The simple model is a special case of the other types. The models consist of central and peripheral components. The most common structure is the mamillary model. The peripheral compartments are linked via micro rate constants to the central compartment. The compartments of the catenary model are arranged in a chain. A typical structure of the mamillary model is shown. 19

CONTROLLER

During the last years much more research power was internationally invested in the development of closed-loop 17th IFAC World Congress (IFAC'08) Seoul, Korea, July 6-11, 2008 9603 controllers which are direct connected with on of the main parts of anesthesia, relaxation, hypnosis or analgesia. A lot of different model-free (e.g.. PID) or modelbased (e.g. GPC) controller were developed and tested in the operating room (Olkkola et al. [1991], Mason et al. [1996], Mahfouf [2006]). The design of controllers for the level of hypnosis is much more difficult because of the non sufficient measurement technique and cross reaction of the hypnotic drug with other drugs. The controller structures range from simple PI- and PID- over model-based to fuzzy-controllers, how to see exemplary in Struys et al. [2001], Absalom et al. [2002], Schwilden et al. [1989]. The cross reactions of the hypnotic and analgesic drugs, described in a previous section were investigated during the last years amongst others like Vuyk et al. [1995], Milne et al. [2003], Kern et al. [2004], Bouillon et al. [2004], Minto et al. [2000]. New controller strategies try to handle both variables

hypnosis and analgesia at the same time as MIMO-controller, see in Nunes et al. [2005], Mahfouf et al. Fig. 2 shows a research system for the controller development. The equipment - anaesthetist interface and valid data collection are important issue. 20 Fig. 2. Components of the research equipment for the development of the Rostocker assistent system for anesthesia control (RAN) 1 Control of the neuromuscular blockade In the current configuration neuromuscular blockade is registered electromyographically using single twitch stimuli with a sampling period of 12s. The original EMGresponses is visualized and registered on-line. The setpoint for the neuromuscular blockade is 90% (T1 = 10% of the signal before drug administration). A model-based adaptive generalized predictive controller (aGPC) was implemented into the "'Rostocker assistant system for anesthesia control"'.In order to get actual patient information an on-line identification of a thirdorder discrete-time ARX-model is implemented. The model is one input for the generalized predictive controller. If the measured T1 has reached the 12% − 0% area around the setpoint, and the onoff controller is working, an online identification starts. 21 Instead of the CARIMA-model, introduced by Clarke et al. [1987], a third order ARX-model will be identified. To compensate small variations in the time delay additional b-coefficients will be modelled, as shown in (5) using MATLABnotation (Mahfouf [2006]). This step was only motivated from the control theory point of view. How to see below a complex pole will originate, which has no pharmacokinetic sense.2 Control of the depth of hypnosisIn the RAN the depth of hypnosis is measured via bispectral index (BISXP-monitor). A Fuzzy-PD+I (P=proportional-, D=differential-, I=integral-part) controller calcu17th IFAC World Congress (IFAC`08) Seoul, Korea, July 6-11, 2008 9604 lates the amount of hypnotic drug propofol witch is necessary to minimize the error between the actual measured BIS-value and the BIS-setpoint of 40 every 5 seconds. The general controller design is given in Fig.3 and details were published in Simanski et al.

II. CONCLUSION

Closed-loop drug delivery in anesthesia is certainly feasible. Unfortunately, most of the described closed-loop technologies have been used under wellcontrolled research conditions. The challenge is now to prove fully the safety and utility for its adaption into clinical practice [92]. Finally, clinicians will have to determine whether or not, adaptive, intelligent computer systems with dual, interacting, closed-loop systems will facilitate better control and improve outcome. The paper tried to explain in a very short way the market and the potential for modeling and control in anesthesia, especially in the field of automatic drug delivery. The most important thing was to transport the idea and the vision: automation in anesthesia my assist and support but not replace the anesthetist. Furthermore constant neuromuscular block precisely adjusted to the individual patient leads to better intraoperative conditions, reduces drug consumption, shortens the postoperative recovery period and finally saves costs. Monitoring the depth of hypnosis may reduce the probability of awareness and drug overdosing. Acknowledgments: M.M.R.F. Struys is supported by a grant from IWT-Flanders for developing closed-loop in collaboration with the Ghent University Department of Engineering, and has grants pending with ECC for closed-loop development. Disclosure: M.M. Neckebroek: none; T. De Smet: none; M.M.R.F. Struys: received compensation from British Journal of Anaesthesia for serving as a board member. The Ghent University holds patent rights on the Bayesian closed-loop controller for propofol administration, described in this article.

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