

Automatic drug delivery in anesthesia - the design of an anesthesia assistant system [★]

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Abstract: The main goals of general anesthesia are adequate hypnosis, analgesia and maintenance of vital functions. For a number of surgical procedures neuromuscular block is essential. Furthermore patient safety and cost reduction as minimized drug consumption and shortened post-operative recovery are main issues and motivation of automation efforts in anesthesia. Since the beginning of the eighties engineers and physician are working together in the field of the development of closed-loop systems for drug delivery. The work gives only a short overview about the development of the automation in drug delivery systems over the last years without the claim of completeness and expressed the much more vision. In the final stage, the designed control system, the so called "Rostocker assistant system for anesthesia control (RAN)" should be fitted out with the possibility to control four different drugs automatically. Currently the multiple-input multiple-output (MIMO) control of the depth of hypnosis and neuromuscular blockade is realized as well as the closed-loop control of deep hypotension. A pilot study for the closed-loop control of analgesia is currently running. The paper points some general remarks and the designed MIMO-system for controlling the depth of hypnosis and the neuromuscular blockade

Keywords: drug delivery, biomedical control, biomedical system, modelling

1. INTRODUCTION AND MOTIVATION

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.

After the application of neuromuscular drugs artificial ventilation is essential. The control of artificial ventilation is also an important research topic but is not an issue in the following chapters. The remarks are restricted to intravenously injected drugs.

More and more new short-acting drugs like mivacurium, propofol and remifentanil are inherent parts in modern anesthesia practice. This requires a continuous mode for drug application and implies the use of automatic control. Precondition for designing a closed-loop control system is an actuator which allows to control the current infusion rate. With the development of remote controllable infusion pumps one barrier on the way to design a control system was vaulted.

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The majority of the used drugs operate not only straight forward to the desired effect. For example the hypnotic drug propofol effects not only on hypnosis level but increase also the analgesia threshold. The same behavior exists in the opposite way for the analgesic drug remifentanil. Remifentanil as an analgesic drug also shows hypnotic effects, which leads to relevant interference effects. Because of the cross-actions between the drugs the anesthetist can adjust the desired level of hypnosis and analgesia with different amount of both drugs. From the control engineering point of view adequate anesthesia is a multiple-input - multiple-output problem (MIMO).

In the daily routine work the anesthetists calculate the necessary drug amount with the help of dose regimes, mostly in relation to the patients body weight. Physicians with more experiences correlate dose regime with observations of the general patient behavior, which is a very complex process.

In the following chapters the steps from measurement to controller design are drafted. Every chapter shows a short historical review before the technology used in the RAN is pointed out. Section 2 describes the problem of measuring the state of relaxation, hypnosis and analgesia. The effect from the drug on the human body should be modeled

for the off-line controller design. One possible strategy for modeling is discussed in section 3. In section 4 the development of several controllers is reflected. Section 5 gives a summary and offers a vision.

2. MEASUREMENT OF RELAXATION, HYPNOSIS AND ANALGESIA

2.1 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 than 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 – 300 μ s 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 T_1 -stimulation, with single twitches. By using the single-twitch stimulation mode (one twitch every 12 sec.) a control value T_0 ($T_1\% = T_1/T_0$) is needed prior to the application of the muscle relaxant. The $T_1\%$ value decreases after an initial bolus injection and the neuromuscular block increases. A typical setpoint can be adjusted at 90% neuromuscular blockade or $T_1=10\%$. In the current configuration we are using a T_1 -stimulated EMG + AMG registration of the neuromuscular blockade.

2.2 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 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 hypnosis the BIS-Monitor A-2000 with "XP-software version" from "Aspect medical systems" was implemented in the RAN.

2.3 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 an analgesia 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.

3. 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 pharmacokinetic-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 in Fig. 1.

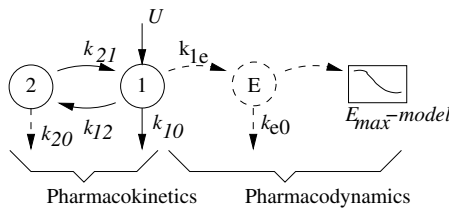


Fig. 1. Mamillary compartmental model structure (Stadler [2003]).

The pharmacokinetics is described by one central compartment, number 1 in Fig. 1, and one or more peripheral compartments, number 2. The peripheral compartments are linked to the central compartment via micro rate constants (k_{xy}). The drug distribution is described by the micro rate constants and by the elimination time constant (k_{10}). For the special way of drug elimination, for example the hofmann elimination, relevant for the drug atracurium, an additional elimination time constant (k_{20}) is helpful. An additional dynamic compartment describes the pharmacodynamics (Weatherley et al. [1983], Sheiner et al. [1979]). The pharmacodynamics are described by an additional dynamic compartment, the effect site compartment (E) and a static dose-effect nonlinearity, the E_{max} -model. The advantage of these models is the relatively small number of adjustable parameters. The concentration of the drug elimination is the main disadvantage of these models. The initial transport and the distribution are only fragmentary implemented.

For the neuromuscular blockade controller the calculation of the following model was deduced from theory showed in Figure 1. The micro rate constant k_{20} is without influence for the used drug mivacurium.

Using the notations $x_i(t)$ for the drug concentration in the i -th compartment at time t , $\dot{x}_i(t)$ for the rate of change and $u(t)$ for the given drug input, the pharmacokinetic model is described by

$$\dot{x}_1(t) = -(k_{10} + k_{12})x_1(t) + k_{21}x_2(t) + u(t) \quad (1)$$

$$\dot{x}_2(t) = k_{12}x_1(t) - k_{21}x_2(t)$$

where k_{10} denotes the elimination rate constant and k_{12} , k_{21} the transfer constants between compartment 1 and 2. A third compartment, the so-called effect compartment

$$\dot{x}_e(t) = k_{1e}x_1(t) - k_{e0}x_e(t) \quad (2)$$

should be appended to the pharmacokinetic equations, as shown by experimental work from (Sheiner et al. [1979]). Combining (2) with (1), and applying Laplace transformation we get the transfer function

$$\frac{X_e(s)}{U(s)} = \frac{K(1 + T_D s)e^{-\tau s}}{(1 + T_1 s)(1 + T_2 s)(1 + T_3 s)} \quad (3)$$

where an additional time delay τ has been introduced to model the transport delay of the drug from the injection point to the receptors. Pharmacodynamics can help to describe the relaxation effect depending on the drug concentration in the blood plasma. The overall non-linear model is obtained by combining the compartment model (3) with the Hill equation (Mahfouf [2006])

$$E_{eff} = \frac{E_{max} X_e^\alpha}{X_e^\alpha + X_e^\alpha(50)} \quad (4)$$

where $X_e(50)$ is the drug concentration at 50% effect of the final value E_{max} , X_e the drug concentration, and α the Hill coefficient.

For modeling of the propofol to BIS interaction the model structure has to be extended with an additional compartment and therefore the order of the model (3) extended to four.

In our case we are using the mamillary PKPD models, parametrized with the help of measured data, for the laboratory simulation and the controller design. Two time 15 patients were measured (15 - neuromuscular block, 15 - depth of anesthesia under standard anesthesia conditions) during simple on-off controller studies. We used simple controller for separate measurements and control of neuromuscular blockade (NMB) and depth of hypnosis (DOH). We split the data into the categories sensitive, normal and non sensitive patients regarding to the reaction (changes in NMB or DOH) of a drug dose. Three models were parametrized for the neuromuscular blockade in reaction of the drug mivacurium and three models were parametrized for the depth of hypnosis as reaction to propofol.

4. CONTROLLER

During the last years much more research power was internationally invested in the development of closed-loop

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 model-based (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. [2005].

Fig. 2 shows a research system for the controller development. The equipment - anaesthetist interface and valid data collection are important issues.

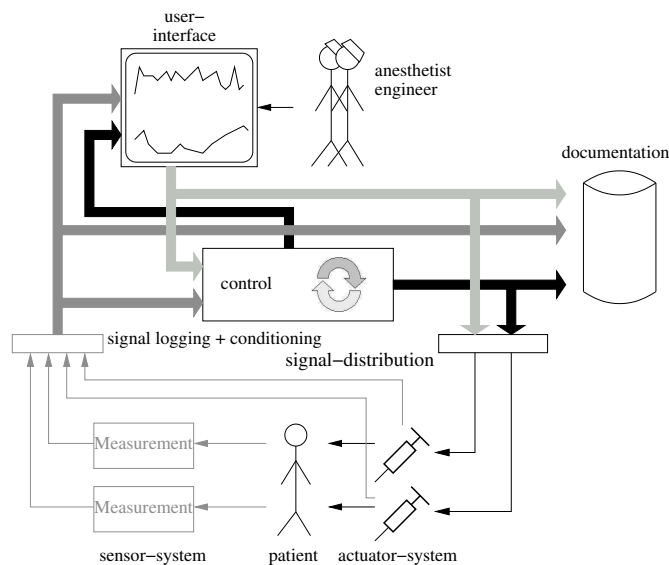


Fig. 2. Components of the research equipment for the development of the "Rostocker assistant system for anesthesia control (RAN)"

4.1 Control of the neuromuscular blockade

Fig. 4 shows the structure of the multiple-input multiple-output system for the control of neuromuscular blockade and depth of hypnosis used in the "Rostocker assistant system for anesthesia control (RAN)".

In the current configuration neuromuscular blockade is registered electromyographically using single twitch stimuli with a sampling period of 12s. The original EMG-responses is visualized and registered on-line. The setpoint

for the neuromuscular blockade is 90% ($T_1 = 10\%$ 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 third-order discrete-time ARX-model is implemented. The model is one input for the generalized predictive controller. If the measured T_1 has reached the 12% – 0% area around the setpoint, and the on-off controller is working, an online identification starts. 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 MATLAB-notation (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.

$$G(q) = q^{-5} \frac{b_0 + b_1q^{-1} + \dots + b_5q^{-5}}{1 + a_1q^{-1} + a_2q^{-2} + a_3q^{-3}} \quad (5)$$

This model will be identified online at each sample, every 12s. For instant, the following parameters were found for one patient at the endpoint of control:

$$\begin{aligned} \hat{a}_1 &= -0.3595, & \hat{a}_2 &= -0.3310 \\ \hat{a}_3 &= -0.294, & & \\ \hat{b}_0 &= 0.0131, & \hat{b}_1 &= 0.0025 \\ \hat{b}_2 &= 0.0520, & \hat{b}_3 &= -0.0346 \\ \hat{b}_4 &= 0.0677, & \hat{b}_5 &= -0.03 \end{aligned}$$

As consequence of the small sampling period $T_s = 12s$, a numerical problem exists and leads to the pole near to the point 1. At the same time the \hat{b} -parameters show a high fluctuation and a non-minimum-phase model will be identified. Because of the measurement noise the idea with the additional \hat{b} -parameters doesn't work in the desired way. The chosen adaptive Generalised Predictive Controller, aGPC, can handle all these problems, how explained in Clarke et al. [1987].

During the control the forgetting factor of the parameter identification will change from 0.95 at the beginning of the identification with the active on-off controller to 0.99 during the work of the aGPC. With the help of the typical movement of the signal during the on-off controller phase a good parameter convergence is available. After the second falling flank of the on-off controller and a minimal infusion time of 3 min a switch from the on-off controller to the aGPC is permitted.

With the GPC and the chosen strategy an adaptive and robust control system could be realised. Figure 5 shows an example of neuromuscular blockade control. The measured EMG and mivacurium infusion rate are illustrated.

4.2 Control of the depth of hypnosis

In the RAN the depth of hypnosis is measured via bispectral index (BIS-XP-monitor). A Fuzzy-PD+I (P=proportional-, D=differential-, I=integral-part) controller calcu-

lates the amount of hypnotic drug propofol which 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. [2003].

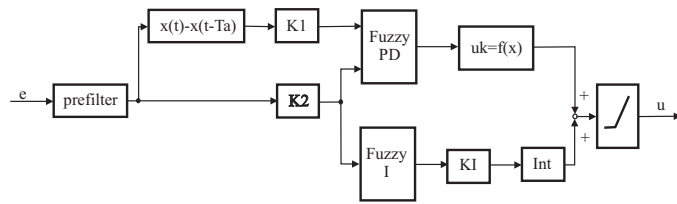


Fig. 3. Design of the Fuzzy-Controller, Kx are scaling-factors

Fig. 5 shows an exemplary control. The setpoint for the neuromuscular blockade ($T1 = 10\%$) is illustrated together with the measurement signal in the upper figure. Below the measurement signal the infusionrate of mivacurium as neuromuscular drug calculated from the adaptive Generalized predictive controller (aGPC) was plotted. The both of the lower figures show the measured BIS-index and the infusionrate for the hypnotic drug propofol.

Current research work is concentrated at the development of an automatic controller for controlling the analgesia level and to replace the anesthetist as "analgesia-controller". Currently a fuzzy expert system to control the analgesia level with the help of HRV and blood pressure measurement is under construction.

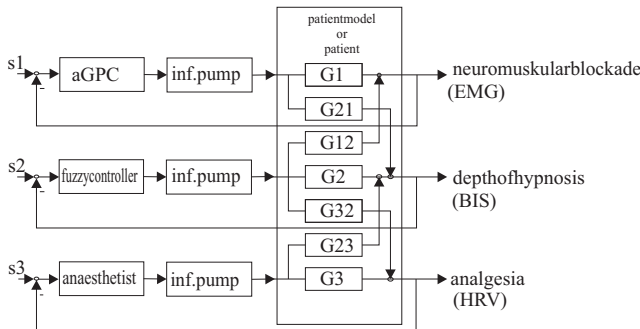


Fig. 4. Structure of the Multiple-Input Multiple-Output system used in the "Rostocker assistent system for anesthesia control (RAN)".

5. SUMMARY

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. Therefore "The International Task Force on Anesthesia Safety [1993]" expanded

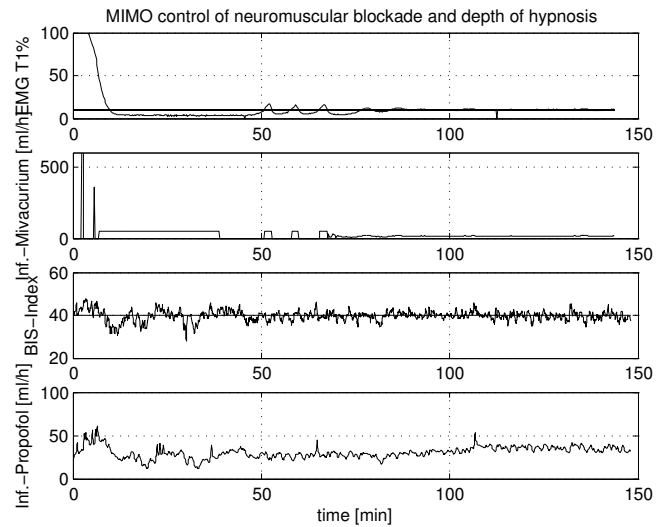


Fig. 5. Sample of a MIMO control of neuromuscular blockade and depth of hypnosis with RAN. Real data measurement during abdominal surgery at the operating room at the University of Rostock.

in 1993 the term of anesthesia monitoring. The monitoring of hypnosis and neuromuscular function are described as essentials of adequate intraoperative monitoring.

The developed MIMO control system was tested under real time conditions at the operating room. In a first study, published in Janda et al. [2006], 22 adults patients were controlled. Furthermore the neuromuscular blockade controller was successfully tested during a liver transplantation of more than 8 hours.

The vision of the research efforts described is the design of an anaesthetic assistant system comparable to the autopilot in commercial airliners.

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