MEASUREMENT AND CONTROL OF NEUROMUSCULAR BLOCKADE AND DEPTH OF ANAESTHESIA

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Abstract. *The paper considers control problems for neuromuscular blockade and depth of anaesthesia. The control system is intended to be used in controlling the main parts of general anaesthesia. The applied measurement techniques, experimental conditions and control strategies are presented. The results of a study with* 31 *patients for the control of neuromuscular blockade, and first trials for* 6 *patients for the control of depth of anaesthesia are listed.*

1 Introduction

The activities of anaesthetists include numerous repeated and isolated tasks. Anaesthetists have to observe and control a great number of different variables of anaesthesia, and also some of the vital functions. Anaesthesia means an adequate hypnosis, analgesia and muscle relaxation for suppression of the effects of surgical manipulations.

In each of these areas the main problem consists in measuring. The degree of relaxation can be estimated by different methods, some of them are explained in section 2. The measurement of the depth of anaesthesia is briefly discussed in section 3. Up to now, there are no measurements to quantify the analgesia.The introduction of new short acting compounds needs a continuous mode as for measurement of control variables as for injection of drugs to the patient. The applied control methods for the neuromuscular blockade and the depth of anaesthesia are described in sections 4 and 5. Modelling is a pre-condition for controller design and briefly discussed.

Automatic control of anaesthesia can support the anaesthetist in his activities. The closed-loop control of the depth of anaesthesia suppresses the danger of awareness or drug overdoses. A constant neuromuscular block leads to good working conditions for the surgeons. A shorter stay time of the patient in the postoperative care unit helps saving money.

International leading groups in the area of controller design for use in anaesthesia are working also in Sheffield with Linkens/Mahfouf et. al [6] and Zuerich with Morari/Stadtler et. al [10]. Besides there is a research group in Vancouver with Huzmezan et. al. In contrast to these groups we developed our own measurement device for the neuromuscular monitoring [2, 8], which is briefly described in this paper in the following section. Thereby, we have the possibility to observe the quality and quantity of relevant measurement signals.

2 Measurement of muscle relaxation

As exposed in section 1, one of the main concerns of the anaesthetist in the operating theatre is to monitor and control the muscle relaxation. The evoked muscle responses after neurostimulation can be registered by electromyography (EMG), mechanomyography (MMG) or acceleromyography (AMG).

Depending on the neuromuscular block the anaesthetist maintains the relaxation by additional bolus injections of muscle relaxant. The introduction of new short to ultra-short acting compounds (e.g. Mivacurium) leads to extremely small injection periods. Therefore, a continuous application is necessary to maintain a constant neuromuscular block during anaesthesia.

Besides, the correct choice of the position for the stimulation, the pattern of stimulation and the quality of the stimulator output are very important for monitoring the neuromuscular blockade. The output current of the stimulator has to be constant, irrespective of different skin resistors. The duration of a stimulation impulse should be constant between $200 - 300\ \mu$s. A supramaximal stimulation, where

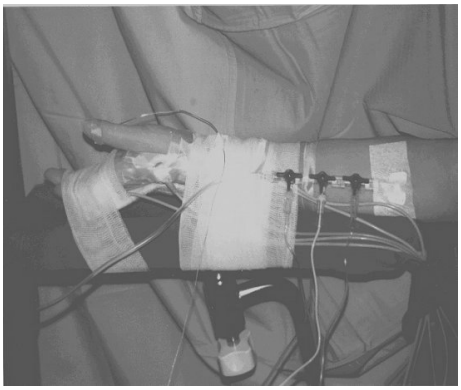
the stimulation current is 20% higher than the stimulation current which leads to the maximal response, is necessary, so that all nerve and muscle fibres are activated.

In our configuration an electrical stimuli with a sampling period of 12 seconds stimulates the nervus ulnaris. The Myotest DBS from Biometer was used as nerve stimulator. The muscle reaction represents the state of relaxation. By using the single-twitch stimulation mode (one twitch every 12 sec.) a control value ($T1/T0$) is needed prior to the application of the muscle relaxant. The $T1$ value decreases after an initial bolus injection, and the neuromuscular block increases.

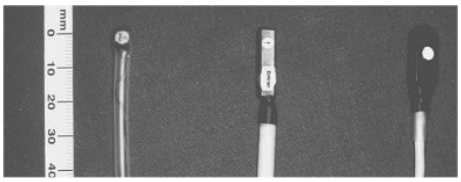
A prerequisite for developing a closed loop system is a high quality measurement of the control signal. Our research group has developed a new device for registering the relaxation state with EMG, MMG and AMG simultaneously. In principle, different peripheral nerves can be used for the neurostimulation. The electromyography is recording the electrical signal that is generated by the muscle action potential under its surface electrodes [8]. The force of the thumb after stimulation can be registered by mechanomyography. The acceleromyography is recording the acceleration of the thumb after neurostimulation. The system allows to observe the quality and quantity of the measured signals. This is one of the greatest benefits of the new developed system in contrast with commercial systems like the NMT-Module from Datex, as producer.

An additional study of the relative comparison of the above three techniques is cited in [2]. With AMG and EMG the neuromuscular blockade could be registered easily. On the other side, control in the operating theatre requires a reliable robust measurement technique and precise signals. Therefore, the neuromuscular block identified by EMG, was used.

Figure 1(a) shows the use of sensors in the operating theatre. Additional acceleration sensors were implemented and tested in the system. So it is possible to use the acceleromyography as additional information for the neuromuscular blockade. The EMG-electrodes and one AMG-sensor is visible in Figure 1(a). Figure 1(b) shows the tested acceleration sensors. At the extreme right of Figure 1(b) a commercial sensor from Biometer is shown. In the middle of the picture a two-dimensional piezoresistive acceleration sensor is shown. The use of a two-dimensional sensor is improving the quality of the measurement signal, because the movement of the thumb is not strictly limited in one direction. The sensor at the left side of Figure 1(b) is a piezoelectric acceleration sensor, which was used for different muscles.



(a) Measurement of NMB with EMG and AMG



(b) Implemented AMG-Sensors

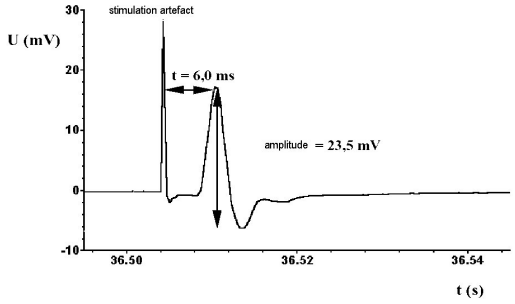
Figure 1: Measurement of the neuromuscular blockade via EMG and AMG

The sensor is very small and therefore, it is in a good way applicable for children or small muscles.

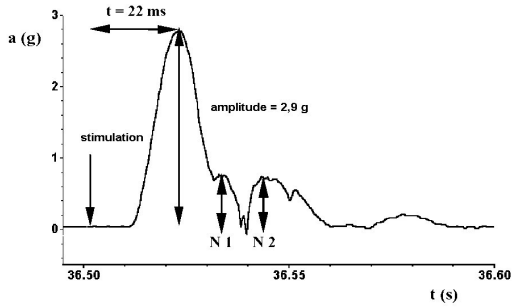
The control quality depends directly on the quality of the measurement signal, Figures 2(a) and 2(b) show examples for the EMG- and AMG-signal. The evoked sum action potentials were registered by means of especially made stainless steel electrodes with a diameter of 15 mm. A minimum signal amplitude of 10 mV for the electromyography and approximately 1 g for the acceleromyography is required for a reliable control. The place of stimulation and measurement electrodes should be located carefully. The same is also valid for the acceleration sensor.

The stimulation impulse is reflected in the measurement of the EMG signal as a sharp peak, as clear in the Figure 2(a). A time window of suitable width, starting at a time when the stimulation artefact has been decayed is chosen for calculation of $T1/T0$. A time window fade out the stimulation artefact for calculation of the measurement value $T1/T0$. The AMG-signal is without stimulation artefact but with additional maxima N_1 and N_2, which have no influence on the result. A time delay of 6 ms for the EMG and 22 ms for the AMG between stimulation and measurement signal has been found as per the physiology of neuromuscular transmission.

The use of the mechanomyography in daily practical work in clinics is very expensive.



(a) Example for an EMG signal



(b) Example for an AMG signal

Figure 2: Example signals for EMG and AMG

3 Measurement of depth of anaesthesia

The anaesthetist uses different parameters to estimate the depth of anaesthesia, some of them like tearing and sweating are not measurable. However, automatic control of depth of anaesthesia needs measurable outputs. A direct measurement of the hypnosis is not yet available.

Depth of hypnosis is expected to be reflected in the electroencephalogramm (EEG). Different algorithms are known for estimation of residuals as indicator for depth of anaesthesia from the raw EEG. The main disadvantage of the EEG measurement is its variation with different anaesthetic agents.

One group of measurement methods based on the power spectrum. The complexity of the raw EEG is decreasing with an increasing depth of anaesthesia. The spectral edge frequency 95% (SEF 95) determines a frequency limit, such that 95% of the signal power corresponds to frequencies up to this limit. The median frequency corresponds to the 50% of the power spectrum. The edge frequencies decrease with the increase in depth of anaesthesia. The correlation between the spectral edge frequencies and the depth of anaesthesia is not clearly defined. The use of the SEF as valid measurement for the depth of anaesthesia is contentious [11].

The bispectral index (BIS) has become very popular during 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 by a simple variable. A good correlation of the BIS with the plasma concentration of Sevoflurane was described by Widman [11]. Different versions of the so-called BIS-monitor from Aspect Medical Systems vary a lot in measurement and can not be compared.

Another measurement procedure is the measurement of the response of the EEG to stimulation. The evoked potentials reflect the subjective clinical signs that anaesthetists use. The evoked potentials are indicators of the response of the central nervous system (CNS). Auditory evoked potentials (AEP) are used in different applications [5].

In the presented study, the BIS-monitor Aspect A-2000 was used for recording the EEG and to estimate the depth of anaesthesia. The daily clinical use is simpler than the use of the AEP.

4 Closed loop control of muscle relaxation

In order to get a theoretical model of the muscle relaxation process pharmacokinetic and pharmacodynamic data has to be available. Pharmacokinetics describe the interaction between drug dose and drug concentration in the blood plasma and in other parts of the body. For modelling the relaxation process a conventional two-compartment model is used. 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

$$\begin{aligned} \dot{x}_1(t) &= -(k_{10}+k_{12})x_1(t) + k_{21}x_2(t) + u(t) \\ \dot{x}_2(t) &= k_{12}x_1(t) - k_{21}x_2(t) \end{aligned} \tag{1}$$

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

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

should be added to the pharmacokinetic equations, how experimental work has shown [7].

Combining (2) with (1), and applying Laplace transform we get the transfer function

$$\frac{X_e(s)}{U(s)} = \frac{K(1+T_0 s)e^{-\tau s}}{(1+T_1 s)(1+T_2 s)(1+T_3 s)} \tag{3}$$

where an additional dead time 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 [6].

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

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. After data collection a theoretic model optimization (TMO) leads to a simulation model. Due to the nonlinear behavior of the process nonlinear control methods should be used. Additionally the controller should be robust against model uncertainties. During the operation the behaviour of the patient could change and every patient is different from others. Therefore, an adaptive algorithm should be used. The Generalised Predictive Control (GPC), successfully used in biomedicine by *Mahfouf* [6], realizes major parts of the requirements. To build an adaptive control strategy, the GPC was extended with a recursive parameter estimation for the patient model. So a nonlinear adaptive strategy was used [8]. The GPC in the original form, as developed by *Clarke* [1] is not a nonlinear control strategy. Therefore, a linearisation around the set point is necessary. The control strategy is divided into two parts. At the beginning of drug injection, the patient behavior is highly nonlinear. Therefore, a bolus of drug is injected to the patient by a modified on-off controller. After identifying the linear model around the operating point, the GPC takes over the control. During the calculation of the control signal, the GPC has to minimise the following criteria

$$J(N_1, N_2, NU, \lambda) = E[(Q_1 + Q_2)] \tag{5}$$

with

$$\begin{aligned} Q_1 &= \sum_{j=N_1}^{N_2} [\hat{y}(t+j) - r(t+j)]^2 \\ Q_2 &= \sum_{j=1}^{NU} [\lambda(j)(\Delta u(t+j-1))]^2 \end{aligned}$$

where N_1 the minimum costing horizon, N_2 the maximum costing horizon, NU the control horizon and $\lambda(j)$ the control weighting sequence denotes.

In (5) $\hat{y}(t+j)$ describes the predicted control signal and $r(t+j)$ the future setpoint.
In order to get actual patient information an online identification of a third-order discrete-time ARX-model is implemented. With the GPC and the chosen strategy an adaptive and robust control system could be realized. Figure 3(a) shows an example of neuromuscular blockade control. Figure 3(a) shows additionally the border of $\pm\, 3\%$ around the set point. In section 6 detailed information about the study are presented.

5 Closed loop control of depth of anaesthesia

The controlled plant, like in case of neuromuscular blockade, consists of three parts: a drug application unit, the patient, and a measurement unit. In the study the liquid drug Propofol and the BIS-monitor as measurement device were used. A remote controllable anaesthetic gas dosage is not yet commercially available.

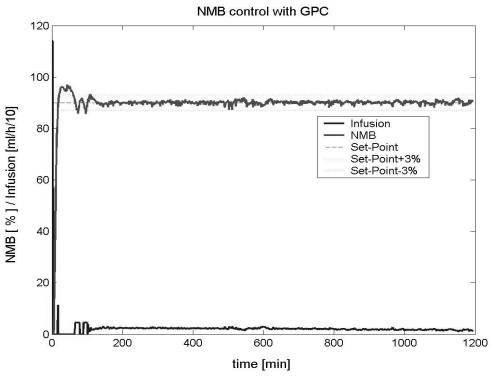
For the application of liquid drugs, there exist two systems, infusion pumps and infusion pumps combined with a drug distribution model. The latter are called target controlled infusion systems (TCI) and have been used in a number of open and closed loop works [4]. The TCI system calculates the necessary infusion value with regard to a target blood concentration.

The described controller estimates an infusion value in mg/kg/h, this value is mapped to the infusion rate. The Graseby 3400 syringe pumps as actuator make an error for low infusion rates, so we use a linearising correction function for the infusion value.

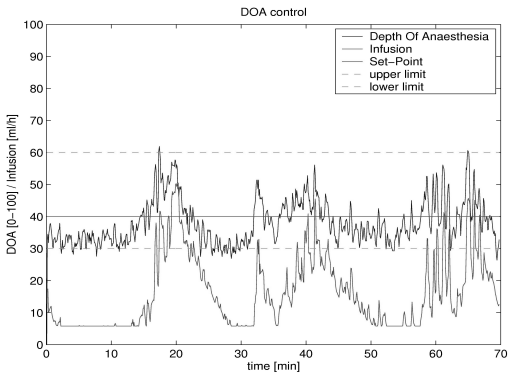
A universal controller for the depth of anaesthesia has to manage different types of patients. For this goal, there are two main strategies possible - the design of robust controllers or a model predictive controller. In absence of a well fitting model, the robust approach seems to be the better choice. Fuzzy controllers are known for stable and robust control, and they can be developed without numerical models.

After the use of a simple on-off controller for model parameter estimation purposes, a fuzzy controller was build on the base of expert knowledge. A prefilter determines the dynamically filtered and normalized control error and derivative of control error. The fuzzy system has two output variables. One variable corresponds to a PD controller output, the other one corresponds after summing up to an integral controller output, see Figure 4. This two values are combined to the controller output signal [9].

The estimated controller output signal additionally contains a nonlinear lower bound with 2 mg/kg/h. This was introduced to avoid stability problems with



(a) Example of neuromuscular blockade (NMB) control



(b) Example of depth of anaesthesia control (DOA) control

Figure 3: Control of neuromuscular blockade and depth of anaesthesia

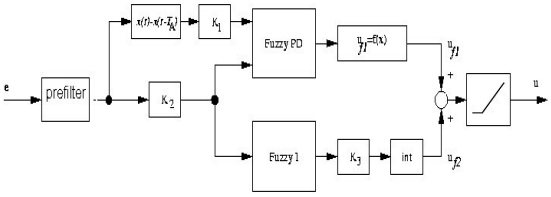


Figure 4: Design of the Fuzzy-Controller

high sensitive patients. Figure 3(b) shows an example of depth of anaesthesia control.

6 Results

The described methods have been successfully applied to different types of patients. With the combination of an on-off controller and GPC the neuromuscular blockade could be controlled with a satisfying accuracy.

parameter	**mean value ± SD**	**Min**	**Max**
settling time [min]	$33,81 \pm 14,5$	$10,20$	$81,60$
t_{max} [min]	$14,50 \pm 12,2$	$4,62$	$56,17$
mean neuromus. blockade [%]	$90,07 \pm 0,2$	$89,46$	$90,54$
RMSD [%]	$1,58 \pm 1,1$	$0,50$	$4,99$

Table 1: Quality of control of the neuromuscular blockade

In Table 1 the results of the study are summarized. The study was performed on a total of 31, classified in ASA 1-3 (American Society of Anesthesiologists), patients aged 33 to 63 which had to undergo a pancreas operation at the Surgical Clinic of the University of Rostock. Patients with additional problems of big influence to the behavior were excluded from the study. A further exclusion criterion was the deviation of more than $\pm$ 20% from "ideal body weight". The aim was to achieve control of the neuromuscular blockade at a setpoint of 90% ($T1_{10}$) within a tolerance range of $\pm$ 3% using the drug Mivacurium. The parameter statistics are listed in Tables 1 and 2. They show the time duration of control. The mean time of control was $391 \pm 89,8$ min.

parameter	**mean value ± SD**	**Min**	**Max**
on-off-controller start [min]	$10,6 \pm 6,9$	$4,6$	$25,5$
on-off-controller duration [min]	$14,2 \pm 7,1$	$6,2$	$37,5$
aGPC start [min]	$24,8 \pm 9,1$	$10,8$	$51,3$
aGPC duration [min]	$375,8 \pm 90,9$	$204,6$	$515,8$
time of control [min]	$391,2 \pm 89,8$	$214,0$	$525,2$

Table 2: Timetable of the control of the neuromuscular blockade

Figure 3(a) shows the control result that were accepted by the specialists.
For the control of the depth of anaesthesia an actual study is running. Till now 6 patients were successfully controlled. Of course, meaningful statistics are not possible with such a small number of patients. So it is only an information that a mean error of $4,73 \pm 0,69$ for the BIS value was noted. The setpoint was changed from patient to patient, therefore the mean error is an appropriate parameter.

The control of the depth of anaesthesia appears in Figure 3(b). Between 15 min and 25 min was a strong pain suspected, because the blood pressure also increase dramatically. The control is quite good in the first 15 minutes and in region from 45 min till 60 min without big painful activities from the sur-

geons. In addition the control of analgesia is necessary to get good results in the control of the depth of anaesthesia.

Nevertheless, it is possible to say that the fuzzy logic controller is able to control the depth of anaesthesia in the operating theatre. Other strategies for the control of the depth of anaesthesia are presented by *Stadler et al.* [10], but using anesthetic gases.

7 Conclusion

As prerequisite for good control of the neuromuscular blockade a uniform measurement system was produced. So, at first time the 3 techniques MMG, EMG and AMG were compared simultaneously. Based on this system controllers for neuromuscular blockade and for depth of anaesthesia were developed.

Both developed controllers have proven to be robust against intraoperative disturbances. The controllers are able to remove steady state control errors [3]. This is an important feature, because the process gain varies from patient to patient and disturbances during the surgery, e.g. heavy blood loss.

The presented results show, that a model-based predictive controller like the GPC can use successfully in biomedicine. Prerequisite is a good patient model around the setpoint. If this model is not acceptable, like in the presented case the model of the depth of anaesthesia, a robust structure could be useful. But than the control quality decrease.

For control of the depth of anaesthesia is important an adequate analgesia, because the crossreactions are not negligible.

8 Acknowledgment

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