

MODELLING AND CLOSED-LOOP CONTROL OF SKELETAL MUSCLE RELAXATION DURING GENERAL ANAESTHESIA USING MIVACURIUM

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Abstract

During general anaesthesia drugs are administered to provide hypnosis, ensure analgesia and skeletal muscle relaxation. In this manuscript the main components of a newly developed controller for skeletal muscle relaxation are described. Muscle relaxation is controlled by administration of neuromuscular blocking agents. The degree of relaxation is assessed by supramaximal stimulation of the ulnar nerve and measuring the electromyogram response of the adductor pollicis muscle. For closed-loop control purposes a physiologically based pharmacokinetic and pharmacodynamic model of the neuromuscular blocking agent mivacurium is derived. The model is used to design an observer based state feedback controller, which is validated in clinical trials. As presented, the controller was able to maintain a preselected degree of muscle relaxation with excellent precision.

1 Introduction

During general anaesthesia administering a neuromuscular blocking agent, such as mivacurium, ensures skeletal muscle relaxation. Several authors describe automatic control of neuromuscular block for several drugs (e.g. [1, 9, 11, 13]). However, to our knowledge only two studies exist with mivacurium ([8] and [10]), where in the first case an adapted model for atracurium was used with an adaptation algorithm to quantify the drug input function. In the latter case a non-linear model based on neural networks was used with an optimizer function to quantify the drug input function. In all protocols supramaximal train-of-four (TOF) stimulation was applied to the ulnar nerve through surface electrodes and the response of the adductor pollicis muscle measured by accelerometric, electromyographic or electromechanic procedures. The first twitch response in relation to a previously calibrated reference twitch is used as the controlled variable ($T1\%$).

Several authors report difficulties in modelling short acting drugs like mivacurium using mamillary compartmental pharmacokinetic pharmacodynamic (PKPD) models (e.g. [7, 15]).

Mamillary compartmental PKPD models assume instantaneous mixing and do not account for recirculation phenomena making them especially ill suited for the description of fast distribution processes (< 2 minutes). This will lead to poor closed-loop performance of mamillary compartmental PKPD model based controllers. This was confirmed by pilot studies with a mamillary compartmental PKPD model based controller which showed divergent results to prior simulations. Also oscillations caused by large inter patient variability and noise sensitivity were detected. Therefore, a physiologically based pharmacokinetic pharmacodynamic model was developed and an observer based state feedback controller implemented. The model is based on a similar model for volatile anaesthetics, which is summarized in [4]. The newly designed controller provided excellent intraoperative control of muscle relaxation during general surgery.

2 Physiologically based compartmental model

2.1 Pharmacokinetics

In Figure 1 the model structure is shown. The model consists of

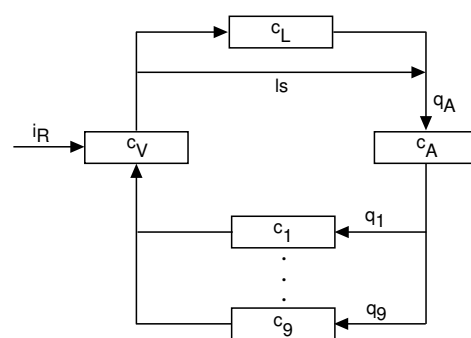


Figure 1: Physiologically based pharmacokinetic model with compartments corresponding to venous blood pool (c_V), lung (c_L), arterial blood pool (c_A), myocard (c_1), brain gray matter (c_2), brain white matter (c_3), well perfused organs (c_4), poorly perfused organs (c_5), stomach and intestine (c_6), skeletal muscle (c_7), fat (c_8) and skin shunt (c_9). The corresponding blood flow through the compartment is described with q_i . The lung shunt is denoted with l_s .

an arterial and venous blood pool and several organ compartments which are further subdivided into a local blood pool and the respective organ tissue. The fractions q_i of cardiac output flowing through each compartment can be calculated according to [4]. Mivacurium is directly infused in the venous blood pool (i_R). The apparent volume of the compartment depends on the blood volume $V_{i,b}$ and the tissue volume $V_{i,t}$, which are known from [4], as well as the ability of the tissue to bind drug. From [16] the apparent volume of drug distribution is described by

$$V_i = V_{i,b} + \frac{\lambda_{i,t}}{\lambda_{i,b}} V_{i,t} \quad (1)$$

where $\lambda_{i,t}$ and $\lambda_{i,b}$ describe the free fraction of drug in tissue and in blood for the corresponding compartments. The tissue/blood partition coefficients $\lambda_i = \lambda_{i,t}/\lambda_{i,b}$ are used to tune the model. The model parameters can be classified as drug specific and drug independent (=physiologically based). Physiological parameters obviously cannot be used to "tune" the model to individual drug characteristics. Therefore, in order to obtain close resemblance of the model output to experimental concentration data, the partition coefficient of mivacurium was empirically adjusted.

Instant equilibration between blood and tissue concentrations is assumed and therefore the concentration of mivacurium in the compartments $c_i(t)$ is described by the standard approach (Equation (2) for all parallel compartments $i \in [1, 2, \dots, 9]$):

$$\frac{dc_i(t)}{dt} = \frac{q_i}{V_i} \{c_A(t) - c_i(t)\} - \kappa_i \frac{V_{i,b}}{V_i} c_i(t) \quad (2)$$

And analogously, $c_L(t)$, $c_A(t)$ and $c_V(t)$ are described by Equations (3), (4) and (5) respectively.

$$\frac{dc_L(t)}{dt} = \frac{q_L}{V_L} \{c_V(t) - c_L(t)\} - \kappa_L \frac{V_{L,b}}{V_L} c_L(t) \quad (3)$$

$$\frac{dc_A(t)}{dt} = \frac{q_A}{V_A} \{l_s \cdot c_V(t) + (1 - l_s) \cdot c_L(t) - c_A(t)\} - \dots - \kappa_A \frac{V_{A,b}}{V_A} c_A(t) \quad (4)$$

$$\frac{dc_V(t)}{dt} = \frac{1}{V_V} \left\{ \sum_{i=1}^9 q_i \cdot c_i(t) - q_A \cdot c_V(t) \right\} - \dots - \kappa_V \frac{V_{V,b}}{V_V} c_V(t) + \frac{i_R(t)}{V_V} \quad (5)$$

Where $\kappa_i \frac{V_{i,b}}{V_i}$ describes the elimination of the drug from the compartments. In the specific case of mivacurium, which is hydrolyzed by pseudo cholinesterase into inactive metabolites in the blood, all κ_i are equal ($\kappa = \kappa_i$). However, only in the blood part of the compartment mivacurium is metabolized, and therefore κ is scaled with $V_{i,b}/V_i$.

2.2 Pharmacokinetic tuning

The parameters κ can be derived from the elimination half-life, which is known for mivacurium. Mivacurium consists of three different isomers, which have different characteristics. In Table 1 the relative fractions and effects as well as the elimination half lifes for each isomer are reproduced from [2]. For pharmacological investigations only the two active isomers are considered [3].

Isomer	rel. Fraction	rel. Effect	$T_{1/2}$
trans-trans	52-62%	1	1.9 min
cis-trans	34-40%	1	1.8 min
cis-cis	4-8%	1/10	52.9 min

Table 1: Composition of mivacurium

An average elimination half-life can be derived by $0.4 \cdot 1.8 + 0.6 \cdot 1.9 \approx 1.9 \text{ min}$, yielding $\kappa = \frac{\ln(2)}{T_{1/2}} \approx 0.37 \text{ min}^{-1}$. Similar values for the elimination half-life (2-3 minutes) can be found in [5] and in [12] where in the latter age dependant $T_{1/2}$ are given.

Additional model independent descriptors of pharmacokinetics and pharmacodynamics are onset time, i.e. time to maximal block after an administration of a specific bolus, and by recovery times, i.e. the elapsed time before the block returns to 25% (T_{25}) or to 95% (T_{95}). The onset and recovery times are given in [14], similar values are stated in [3]. The onset time corresponds to the time at which the concentration at the effect site/biophase peaks after a bolus and can therefore be used to empirically determine λ_i for the respective tissue compartment. For a given volume and perfusion of the compartment the partition coefficient λ_i determines the time of peak concentration (=peak effect) after a bolus dose. In Figure 2 the onset time shift caused by different λ values is shown. It is obvious to correlate the effect of muscle relaxants with the concentration time course of drug in the muscle compartment. Each compartment is described by a specific λ_i , which are in general not equal. However, the pharmacokinetic characteristics of mivacurium shows two distinct decay rates (distribution and terminal elimination half-life). By setting equal λ_i ($\lambda_i = \lambda$) the time course shows the same two distinct decay rates. Therefore, λ

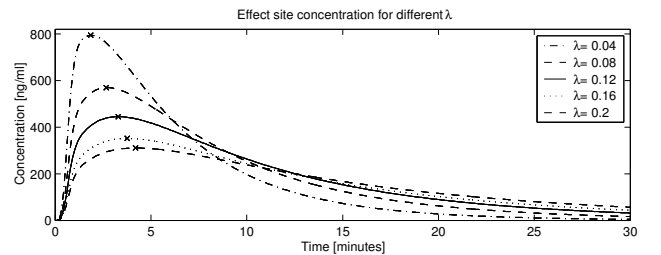


Figure 2: Simulated time shift of peak effect site concentration caused by different λ values

was altered until the correct onset time was obtained for the muscle compartment in simulations ($\lambda = 0.3$). For a bolus dose of 0.15 mg/kg the onset time is 3.3 minutes [14].

2.3 Validation of the physiologically based pharmacokinetic model

Non-compartmental analysis and the application of the concept of moments in statistics allows the calculation of parameters which described the main pharmacokinetic characteristics [16]. This was used to verify the derived models by comparing the results with the literature. The main parameters are clearance Cl , i.e. the amount of drug which is eliminated from the body and the apparent volume of distribution at steady state V_{dss} , i.e. a relation between drug concentration of blood or plasma to the amount of drug in the body.

The assumption of equal λ_i values for mivacurium yielded a volume of distribution at steady state (V_{dss}) of approximately 270 ml per kg bodyweight. This corresponds to the notion that mivacurium is distributed in the extracellular water and is in agreement with the published V_{dss} values (from 51 ml/kg in [6] to 488 ml/kg in [12]). Furthermore, the clearance (Cl) was found to be $25.8 \frac{\text{ml}}{\text{kg}\cdot\text{min}}$, which corresponds to the literature ($25.7 \frac{\text{ml}}{\text{kg}\cdot\text{min}}$ in [7] to $68.2 \frac{\text{ml}}{\text{kg}\cdot\text{min}}$ in [12]).

Therefore, further tuning of the model was not attempted.

2.4 Pharmacodynamics

The pharmacodynamics (PD) is described by a standard empirical fractional sigmoid E_{max} model relating concentration at the effect site to drug effect (Equation (6)).

$$T1\% = 100 \left(1 - \frac{C_7^\gamma}{C_7^\gamma + EC_{50}^\gamma} \right) \quad (6)$$

Where C_7 is the concentration in the effect (skeletal muscle) compartment, EC_{50} is the effect site concentration to achieve 50% effect and γ describes the steepness of the sigmoid E_{max} model. The values EC_{50} and γ were determined as follows.

From [3, 14] onset and recovery times (mean and standard deviation) are known and marked in Figure 3. The parameters EC_{50} and γ are tuned such that these values are reproduced by the corresponding bolus response. The derived pharmacodynamic parameters are $EC_{50} = 100 \text{ ng/ml}$ and $\gamma = 7.5$. The EC_{50} and γ values derived do not differ markedly from values given in the literature [7, 15].

As an example the simulated time course of the effect resulting from a bolus of 0.15 mg per kg bodyweight mivacurium is shown in Figure 3.

2.5 Summary of the modelling procedures

We started with a higher order physiological pharmacokinetic model compared to mamillary compartmental PK models for mivacurium, adjusted the elimination constant of mivacurium according to its elimination half-life and determined the partition coefficient for the effect (muscle) compartment using the

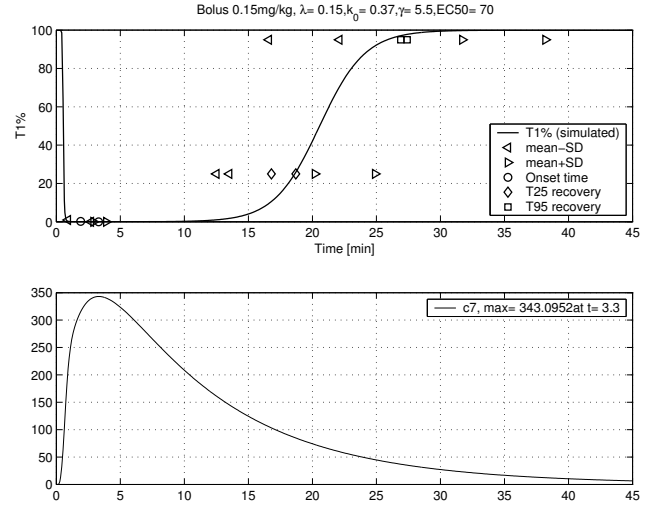


Figure 3: Pharmacokinetic and dynamic simulation for a bolus of 0.15 mg per kg bodyweight. The markers indicate mean onset (\circ) and recovery ($T_{25} = \diamond$ and $T_{95} = \square$) times with the corresponding \pm standard deviation (\triangleleft and \triangleright) as found in [3, 14]. The solid line represents the simulated $T1\%$ time course.

time of peak effect after a bolus dose. Since the assumption of identical partition coefficients for all tissues yielded plausible and supported V_{dss} and Cl [3, 5], we concluded that we identified the most parsimonious physiological PK model. The parameters of a fractional sigmoid E_{max} model were then adjusted using pharmacodynamic data after bolus application.

3 Controller design

In Figure 4 the controller for regulating $T1\%$ is shown. The patient model consists of the linear pharmacokinetics (P) and the nonlinear dose-effect relation (pharmacodynamics). Due to the nonlinear dose-effect relation the controller is compensated to attain approximately unit gain by assuming a pharmacodynamic parameter set of a standard patient. Using this concentration-to-effect relationship the value of C_7 can be approximated (C_{7APP}). The two nonlinearities approximately compensate for deviations of the actual patient's pharmacodynamic parameter set from that of the typical subject. The result-

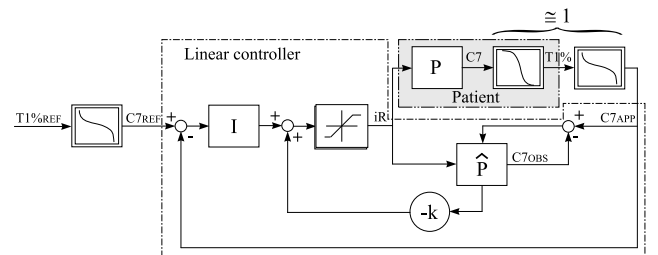


Figure 4: Control structure

ing controller is linear and the controller is designed by solving the LQR problem with an additional integral action.

Routine manipulation of the patient and the clinical equipment may lead to situations where the controller has to be shut down for safety reasons. A major interest lay in developing a controller, which allows to be operated in a clinical environment without interruptions. Special handling of artefacts and measurement failures are necessary. One of these add-on features, the handling procedures used while the syringe is refilled or exchanged, is described by the following anti-windup and bumpless transfer strategy.

Anti-windup and bumpless transfer strategy

In Figure 5 the anti-windup structure is shown. For operating state transition (*man/ctrl*) from manual ($IR_{AUTO} = IR_{MAN}$) to automatic control ($IR_{AUTO} = -k\hat{x} + i$) a standard bumpless transfer structure is used. However, regularly during surgery, the syringe of the infusion pump needs refilling. This typically requires 1..2 minutes. Switching back to manual during this period would reduce the integral action, leading to an infusion rate of zero from where the controller restarts when switching back to automatic control. This produces a deficit of administered drug which then leads to a significant overshoot in $T1\%$. An additional switch (*syringe change on/off*) is inserted after the anti-windup structure. Then the integral action is not reset but stays near its previous value (the integral action is tuned comparatively slow). Also the input IR to the body and the observer is now zero. Therefore, the state variable \hat{x} will decay slowly and therefore the contribution $|-k\hat{x}|$ to IR will decrease. Thus the output IR_{AUTO} of the controller will increase. After the syringe change switch is put to *off* again, this increase in IR partially compensates the deficit in drug delivery during the syringe change.

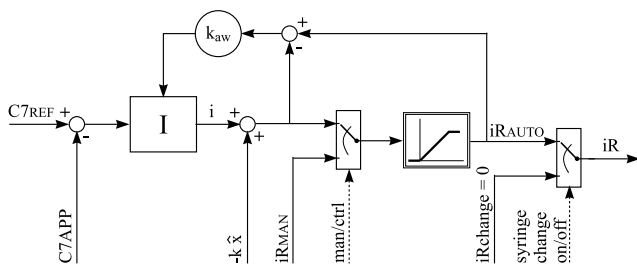


Figure 5: Extended anti-windup structure

Generally wind up is not a desired effect. In this specific case it increases set-point precision as long as the phase of interrupted infusion is not too long. In case the changing of the syringe takes longer than 5 minutes, the system has to be restarted from manual for safety reasons. The anti-windup feedback coefficient k_{aw} is set according to the dead beat condition.

4 Results

4.1 Clinical application

In Figure 6 the clinical application of the controller is shown. The upper plot displays the reference and the measured $T1\%$ values. Additional markers indicate skin incisions (start of actual surgery). In this specific case a first small cut was made by the surgeons for laparoscopy. After minimal invasive surgery was not sufficient a second larger cut followed (laparotomy). At the beginning the measurement is stabilized for more than ten minutes (stabilization phase) where a baseline drift in the measurement can be clearly seen. Generally a base line drift up to 20% can be observed in the first 10 to 20 minutes after induction before the signal stabilizes [17]. After signal stabilization the supramaximal stimulation is re-calibrated. This can be seen by the measurement returning abruptly to 100%. After that the mivacurium bolus is administered to achieve total block for intubation. At 58 minutes the controller was switched on. After 211 minutes the syringe was refilled and due to the compensation effect the time course of $T1\%$ is not visibly affected, further details are shown below.

The $T1\%$ measurement shows sensitivity for disturbances caused by surgical procedures, such as positioning of the patient. For example just after the second skin incision at about 155 minutes several sharp peaks can be seen on $T1\%$. These were caused by an additional surgeon trying to get comfortable at the operating table. Thereby moving the patient's arm which was used for measurements.

By comparing Figures 7 and 8 the effect of the special anti-windup strategy can be seen. In Figure 7 the extended anti-

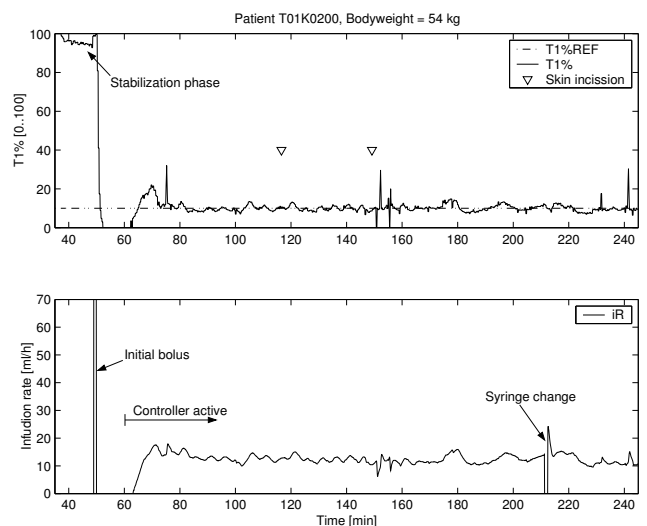


Figure 6: Clinical test regulating $T1\%$. Top: degree of muscle relaxation expressed by the level of depression of the first twitch ($T1\%$, solid) and the corresponding reference ($T1\%_{REF}$, dash-dotted). Lower: Infusion rate (iR , solid) set by the control system.

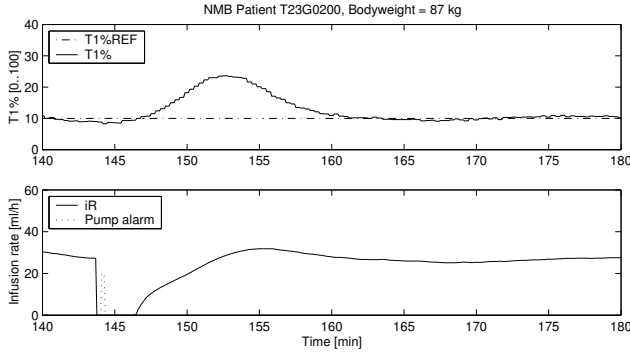


Figure 7: Clinical test regulating $T1\%$ during a phase where the syringe was refilled where the special handling procedures were **not** implemented. Top: degree of muscle relaxation ($T1\%$, solid) and the corresponding reference ($T1\%_{REF}$, dash-dotted). Lower: Infusion rate (iR , solid) set by the control system and the alarm flag received of the infusion pump (Pump alarm, dashed).

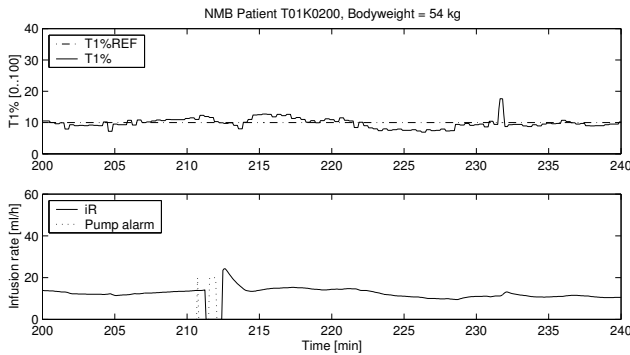


Figure 8: Clinical test regulating $T1\%$ during a phase where the syringe was refilled where the special handling procedures were implemented. Top: degree of muscle relaxation ($T1\%$, solid) and the corresponding reference ($T1\%_{REF}$, dash-dotted). Lower: Infusion rate (iR , solid) set by the control system and the alarm flag received of the infusion pump (Pump alarm, dashed).

windup strategy was not implemented in the control system. The alarm flag of the infusion pump indicates the time where the pump was manipulated and therefore where the infusion of mivacurium was interrupted. The result is a considerable set-point deviation. The effect of the resetting of the integrator is increased as the time lag in the systems dynamics prolongs the time where the infusion is interrupted. In Figure 8 the corresponding incident occurred during a clinical test where the described anti-windup system was active. The difference in performance is apparent. The considerable difference in the infusion requirement between the patients is mainly due to the considerable bodyweight difference. The controller design takes the bodyweight of the patient into account and therefore the results can be compared.

4.2 Performance assessment

Fifteen patients (ASA class I and II) were enrolled undergoing general anaesthesia, two patients had to be excluded from the statistical analysis due to sensor problems and two more because the hand temperature dropped below $32^\circ C$. According to good clinical research practice [17] a low hand temperature influences the measurement procedures. Accumulated time of closed-loop control of the remaining eleven patients was 29.6 hours.

Static performance is expressed by the average absolute deviation (AAD) from set-point and the mean error (ME) from set-point. The AAD is a measure of accuracy and the ME is a measure of bias. Additionally, as an easily understandable measure the percentage of measurements in a range of $\pm\varpi\%$ of set-point ($R_{\varpi\%}$) is derived. The static performance parameters are summarized in Table 2. Note that the set-point was

<i>Param.</i> [<i>unit</i>]	<i>Mean</i>	<i>SD</i>
AAD [$T1\%$]	1.85	0.89
ME [$T1\%$]	-0.28	0.30
$R_{10\%}$ [%]	51.2	18.9
$R_{20\%}$ [%]	72.9	18.6
$R_{30\%}$ [%]	83.1	14.6

Table 2: Static performance parameters.

set at 10 $T1\%$ and therefore ranges of $\pm 10\%$, 20% and 30% correspond to ± 1 , 2 and 3 respectively expressed in $T1\%$.

Additionally, the inter and intra patient variability of the infusion rate was analysed. The mean infusion rate of mivacurium during closed-loop control was 6.97 mg/kg/min and the inter patient range of the observed infusion rates was 3.87 mg/kg/min to 10.20 mg/kg/min. To compare intra patient variability the total time of closed-loop control was divided into segments of 30 minutes and an inter segmental ratio R for each patient j according to Equation (7) was derived.

$$R(j) = \frac{\max[\overline{si_R}(j)] - \min[\overline{si_R}(j)]}{\overline{i_R}(j)} \quad (7)$$

Where $\overline{si_R}(j)$ is the vector containing all mean segmental infusion rates and $\overline{i_R}(j)$ is the overall mean infusion rate of patient j . Intra patient variability derived by the inter segmental ratio R showed a mean of 0.31 and a range between 0.12 to 0.56 over all patients.

5 Discussion and conclusion

In comparison to mamillary compartmental PKPD models [7, 10], which entirely neglect the contribution of circulatory phenomena on drug distribution, the physiologically based PKPD model accounts much better for the initial phase of drug distribution (< 2 minutes after bolus administration). Modelling the distribution is obviously essential for closed-loop control purposes. The benefit of the modified anti-windup structure is apparent as the temporary suspended infusion rate

(i_R) is compensated immediately after restart of infusion, thus the controlled variable $T1\%$ varies only moderately. The measurement of $T1\%$ is prone to movement artefacts caused by passive position changes of the patient's hand used for measurements. No large inter patient variability of the dynamic performance was observed. However, large differences of inter patient and intra patient consumption of mivacurium were observed. This difference resulted in a static or slowly varying offset on the mean infusion rate, which was handled well by the integral action. This is an advantage as drug consumption is minimized and therefore a shorter recovery can be assumed.

A mathematical model for the input output relation of mivacurium was developed which is sufficiently descriptive for control purposes. The designed controller showed excellent results in clinical trials and the control structure allows handling of most clinical incidents (artefacts, loss of signal, syringe change). However, the duration of calibration phase needed to stabilize the $T1\%$ is not tolerable in clinical practice as securing the airway has to be postponed accordingly in the unconscious patient.

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