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 and ensure analgesia and skeletal muscle relaxation. In this paper 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 stimulating the ulnar nerve and measuring the electro-myogram response of the adductor pollicis muscle. For closed loop control purposes a sufficiently descriptive 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 was used in clinical trials on humans. Good results were obtained and are presented.

Keywords:

Anaesthesia, physiologically based modelling, neuromuscular block, model based state feedback

1 Introduction

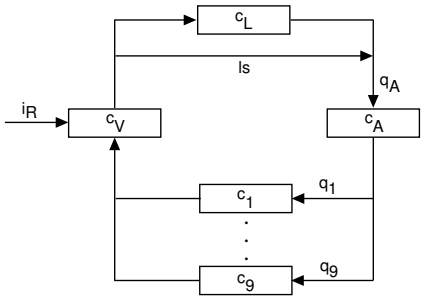
During general anaesthesia administering a neuromuscular blocking agent, such as Mivacurium, ensures skeletal muscle relaxation. Several authors describe automatic control of neuromuscular block for several drugs (e.g. [1, 2, 3, 4]). However, to our knowledge only two studies exist with Mivacurium ([5] and [6]), 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 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 ($T1\%$) as the controlled variable.

Several authors report difficulties in modelling short acting anaesthetic agents like Mivacurium by standard pharmacokinetic pharmacodynamic (PKPD) models (e.g. [7, 8]). Moreover, standard PKPD models are not sufficiently descriptive in the distribution phase and are only used to describe the elimination of the drug. Hence, standard PKPD models are not designed for control purposes where the distribution is essential as well. We were faced with problems when using a PKPD model based controller in clinical trials. The performance showed large differences to expectations formed by prior simulations and clinical results showed oscillating behaviour due to large patient variability and noise sensitivity. By introducing a physiologically based pharmacokinetic pharmacodynamic (PBPKPD) model - which is based on a similar model for volatile anaesthetics [9] - these problems were solved. An observer based state feedback controller was developed and successfully used during general surgery.

2 Physiologically based compartmental model

2.1 Pharmacokinetics

In Figure 1 the model structure is shown. Assuming constant cardiac output CO and mean arterial blood pressure MAP based on population average, the fractions q_i of cardiac output flowing through each compartment are known from [9]. Mivacurium is directly infused in the venous blood pool (i_R). Each compartment consists of two parts, the tissue and the blood part. The tissue stores and the blood transports the drug. The volume of the compartment depends therefore on the blood volume $V_{i,b}$ and the tissue volume $V_{i,t}$, which are known from [9], as well as the ability of the tissue part to uptake the drug. From [9] the volume of drug distribution for



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), skin shunt (c_9), lung shunt (ls)

Figure 1: Physiologically based pharmacokinetic model

volatile anaesthetics is described by

$$V_i = V_{i,b} + \frac{\lambda_{i,t}}{\lambda_{i,b}} V_{i,t} \tag{1}$$

where $\lambda_{i,t}$ and $\lambda_{i,b}$ describe the solubility of the drug in the corresponding compartments and the ability of the tissue to uptake the drug is described by the fraction $\lambda_i = \lambda_{i,t}/\lambda_{i,b}$. The parameters λ_i are used to tune the model concerning the distribution of the drug in the body.

Immediate mixing between blood and tissue part 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 $i \in [1, 2, ...9]$):

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

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

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

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

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

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 $V_{i,b}/V_i$. The parameters κ can be derived from the elimination half-life, which is known for Mivacurium. An average elimination half-life $T_{1/2}$ of Mivacurium is 2.1 minutes [10], yielding $\kappa = \frac{\ln(2)}{T_{1/2}} = 0.31\, min^{-1}$.

The pharmacokinetics are also described by 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 has returned to 25% (T_{25}) or to 95% (T_{95}). The onset and recovery times are given in [11], similar values are stated in [12]. Different drugs do not enter certain tissue parts at all or with different rates. Therefore, every λ_i needs to be derived depending on the compartments characteristics. However, the main compartment of interest is the effect site compartment, in this specific case the muscle compartment and for the rest a rough approximation is adequate. Therefore for simplicity all λ_i are set to the same λ, i.e. the model is tuned to fit the distribution to the effect site only. For a bolus dose of $0.15\,mg/kg$ the onset time is 3.3 minutes [11]. In Figure 2 the onset time shift caused by different λ values is shown, where $\lambda = 0.12$ fits the published PK data best.

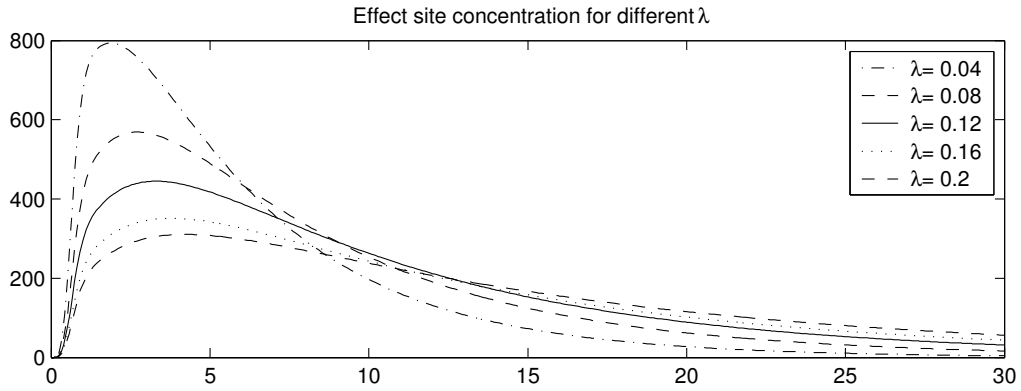


Figure 2: Pharmacokinetic simulations for different λ values

2.2 Pharmacodynamics

The pharmacodynamics (PD) is described by the Hill curve, i.e. the dose-effect relation. The actual skeletal muscle compartment of the PBPK model is the effect site. The specific Hill curve for $T1\%$ is given by Equation (6).

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

Where C_7 is the concentration in the effect site compartment, EC_{50} is the effect site concentration to achieve 50% effect and γ describes the steepness of the Hill curve.

From [11, 12] onset and recovery times 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 $EC_{50} = 100\,ng/ml$ and $\gamma = 3.2$. The EC_{50} and γ values derived do not differ significantly from values given in the literature [7, 8]. As an example

the simulated time course of the effect resulting from a bolus of $0.15\,mg/kg$ Mivacurium is shown.

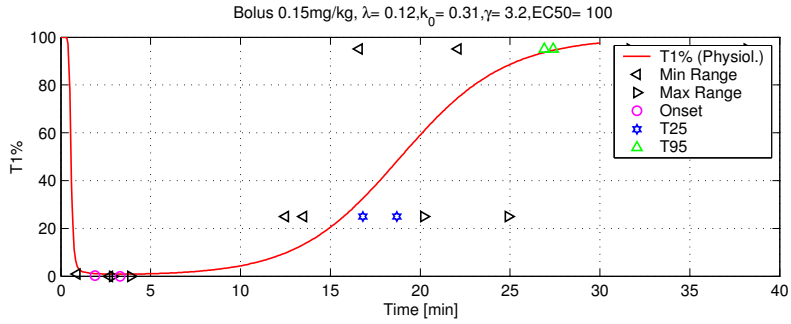


Figure 3: Pharmacokinetic and dynamic simulation for a bolus of 0.15mg/kg

3 Controller Design

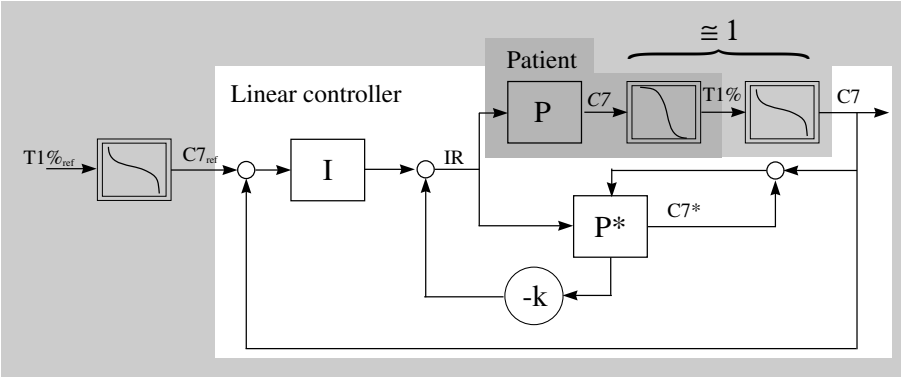


Figure 4: Control structure

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 (Hill curve, pharmacodynamics). Due to the nonlinear dose-effect relation the controller is compensated to attain approximately unit gain by assuming a pharmacodynamics of a standard patient (Figure 4). This estimates the effect site concentration C_7. The two nonlinearities approximately compensate even if the patient variability is large in comparison to the standard patient. The resulting controller is linear and the controller is designed by solving the LQR problem with an additional integral part.

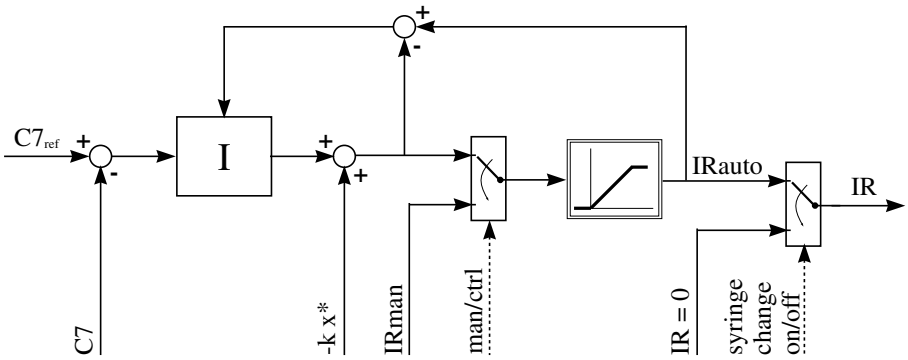


Figure 5: Anti-windup structure

Anti-windup and bumpless transfer strategy

In Figure 5 the anti-windup structure is shown. For operating state transition (*man/ctrl*) from manual ($IR = IRman$) to automatic control ($IRauto = -kx^* + I$) 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 and 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 x^* will decay slowly and therefore the contribution $|-kx^*|$ to IR will decrease. Thus the output $IRauto$ of the controller will increase slowly. After the syringe change switch is put to *off* again, this partially compensates the deficit in drug delivery during the syringe change.

4 Results

In Figure 6 a recording of a clinical test is shown. In the upper plot the reference and the measured $T1\%$ values are shown. Additional markers indicate skin incision (start of 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. At the beginning the measurement is calibrated for more than ten minutes (calibration phase) where a 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

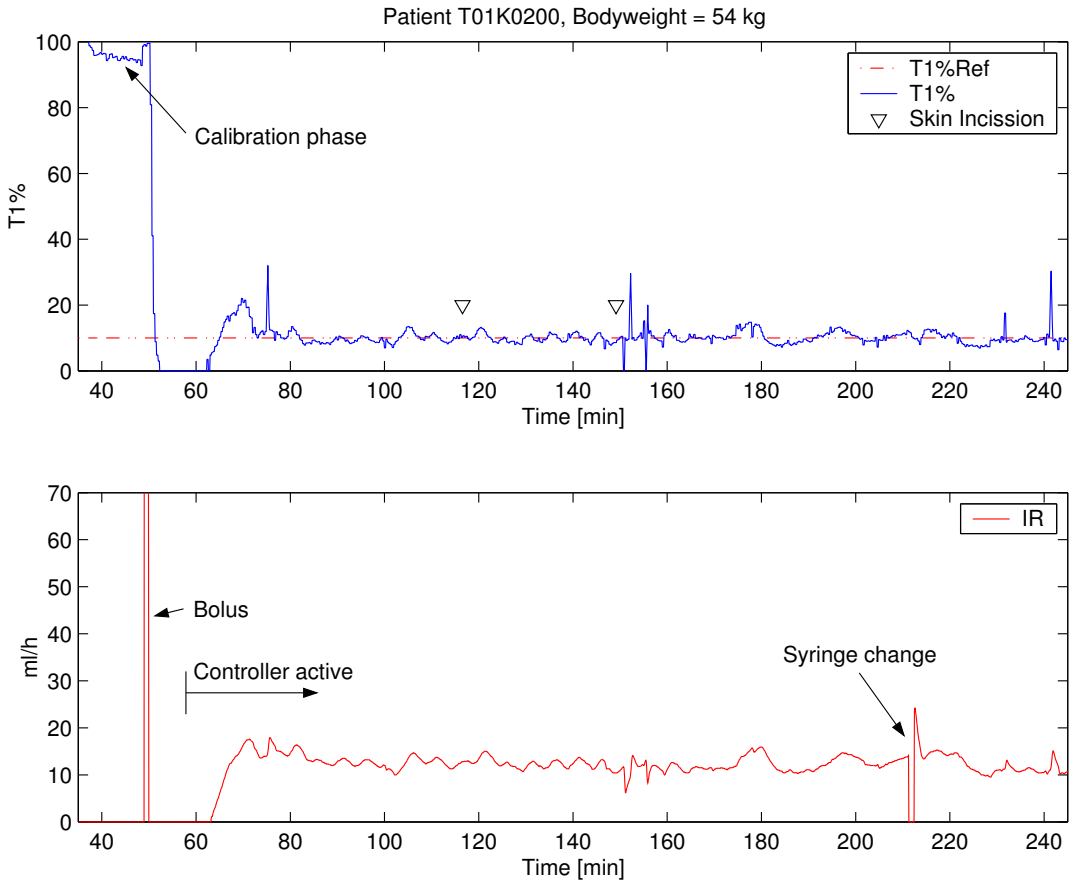


Figure 6: Clinical test regulating $T1\%$

induction before the signal stabilizes. After the signal stabilizes calibration phase is ended and the bolus of Mivacurium is administered to achieve total block for intubation. At about 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.

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 and thereby moving the patient's arm where the measurements were taken from.

Up to date 15 patients were enrolled undergoing general anaesthesia, two patients had to be excluded from the clinical study due to sensor problems. During more than 33 hours the controller was active. The percentage of measurements during automatic control of $T1\%$ in a 10%, 20% and 30% percentile (of set-point) are 50%, 71% and 83% respectively.

5 Discussion and Conclusion

In comparison to standard PKPD models [7, 5], which concentrate on the elimination of the drug only, the PBPKPD model has the advantage of describing the initial phase of drug distribution as well. The distribution is 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 (Figure 6, after 210 minutes), thus the controlled variable $T1\%$ varies only moderately.

The measurement of $T1\%$ is prone to artefacts caused by standard handling of the patient and in particular of the arm of measurement.

No large inter-patient variability of the dynamic performance was observed. However, large differences of inter-patient consumption of Mivacurium were observed. This offset was handled well by the integral action.

For control purposes a sufficiently descriptive model for Mivacurium was developed. The designed controller showed good results in clinical trials and the control structure allows handling of most clinical incidents. However, the calibration phase to stabilize the $T1\%$ is not applicable in clinical practice as the patient needs to be manually ventilated. This increases risk due to non secured air way ventilation.

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