IDENTIFICATION AND CONTROL OF POSITIVE AND COMPARTMENTAL SYSTEMS APPLIED TO NEUROMUSCULAR BLOCKADE

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Abstract: The paper presents a positive control law for feedback stabilization of a particular compartmental system. The features of this system allow to show that the application of the control law leads the system not only to a mass balance but also to a state of equilibrium, thus enabling the tracking of a constant reference. This new approach is used in the framework of neuromuscular blockade control and is illustrated by a simulation study. The problem of embedding identification methods in this compartmental model control approach is also considered and analysed.

Keywords: Compartmental models, positive systems, neuromuscular blockade control, on-line identification

1. INTRODUCTION

Compartmental models are widely used for the modelling of systems in biomedicine, pharmacokinetics (and anaesthesia) and ecology, see Godfrey (1983) or Jacquez and Simon (1993) for particular examples. A compartmental system consists of a finite number of homogeneous, well-mixed subsystems, called compartments, which exchange with each other and with the environment so that the quantity or concentration of material within each compartment may be described by a first-order differential equation. Furthermore compartmental linear systems constitute a subclass of positive linear systems, *i.e.* of systems in which the state and output variables remain nonnegative whatever the positive input sequence might be.

In this paper a compartmental model approach to the control of neuromuscular blockade is considered. During the surgical procedure patients are usually under general anaesthesia, defined as the lack of response and recall to noxious stimuli, reflected in loss of consciousness, pain insensitivity and muscle paralysis. The last one is the subject of the case study presented, its aim being to prevent involuntary muscle movement from disturbing the surgeon's activity. In particular, the higher the precision of the surgery, the higher the quality of the regulation required. Non-depolarising muscle relaxants, such as *atracurium*, act by blocking

the neuromuscular transmission, thereby producing muscle paralysis. The level of muscle relaxation is measured from an evoked EMG at the hand by external electrical stimulation. The requirement of a reliable and robust control system has led to a variety of different control strategies (Lemos *et al.*, 1991; Linkens, 1994; Mendonça and Lago, 1998; Lago *et al.*, 1998; Mendonça *et al.*, 2002). These strategies have proved to be reliable in the maintenance of neuromuscular blockade at the target level, with fairly different doses and anaesthetic techniques, thus showing the system adaptation to individual requirements. However, there still does not exist a theoretical demonstration to this fact.

Recently Haddad *et al.* (2003) proposed an adaptive control law for linear non-negative dynamical systems, and in particular for compartmental systems, with non-negative control and showed, through Lyapunov-based methods, that partial asymptotic set-point stability of the closed loop-system is guaranteed. However, this control law assumes that control inputs are injected into each separate compartment, which is not in accordance with our application. In Bastin and Provost (2002), a positive control law for the feedback stabilisation of a class of positive compartmental systems is proposed in order to guarantee the regulation of the total mass at an arbitrary set point. Here, the same approach as in Bastin and Provost (2002) is used in the framework of neuromuscular blockade control problem. In fact, it is possible to model the *atracurium* as a 3-compartmental pharmacokinetic-pharmacodynamic model with particular features. These features allow to show that the application of the control law proposed in Bastin and Provost (2002) leads the system not only to a mass balance but also to a state equilibrium, thus enabling the tracking of a constant reference.

2. COMPARTMENTAL MODEL AND CONTROL LAW

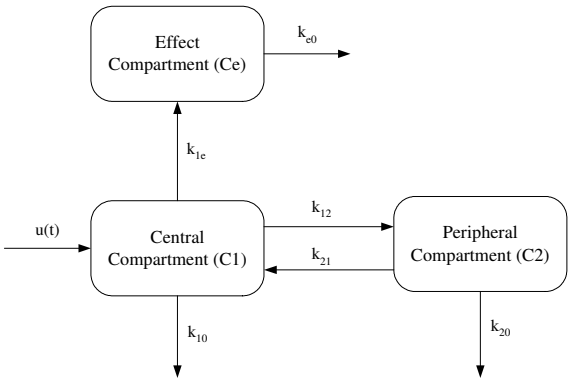

Fig. 1. Block diagram of *atracurium* compartmental model.

The *atracurium* compartmental model can be described by a two-compartment (C1 and C2) pharmacokinetic model combined with an effect compartment (Ce) to model pharmacodynamics as depicted in Figure 1, where $u(t)$ $[\mu g kg^{-1} min^{-1}]$ is the infusion rate administered in the central compartment and $k_{12}, k_{21}, k_{10}, k_{20}, k_{1e}, k_{e0}$ are non-negative micro-rate constants varying from patient to patient. In the pharmacokinetic literature (Weatherley *et al.*, 1983), it is usually considered that the effect compartment has a negligible effect on the pharmacokinetic model so that the drug concentration in the central compartment remains unaffected by k_{1e}. However in this paper k_{1e} will be taken to be nonzero, although very small in comparison with any of $k_{12}, k_{21}, k_{10}, k_{20}$.

In terms of dynamical equations we obtain the following state-space system:

$$\begin{cases} \dot{x}_1(t) &= -(k_{12}+k_{10}+k_{1e})x_1(t) + k_{21}x_2(t) + u(t) \\ \dot{x}_2(t) &= k_{12}x_1(t) - (k_{21}+k_{20})x_2(t) \\ \dot{x}_3(t) &= k_{1e}x_1(t) - k_{e0}x_3(t) \\ y(t) &= x_3(t) \end{cases} \tag{1}$$

where $x_1(t)$, $x_2(t)$ and $x_3(t)$ are the drug concentrations in the central, peripheral and effect compartments, respectively. Rewriting (1) in matrix form yields:

$$\begin{cases} \underbrace{\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix}}_{\dot{X}}(t) = A \underbrace{\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}}_{X}(t) + \underbrace{\begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}}_{B} u(t) \\ y(t) = \underbrace{\begin{bmatrix} 0 & 0 & 1 \end{bmatrix}}_{C} \underbrace{\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}}_{X}(t) \end{cases} \tag{2}$$

where

$$A = \begin{bmatrix} -(k_{12}+k_{10}+k_{1e}) & k_{21} & 0 \\ k_{12} & -(k_{21}+k_{20}) & 0 \\ k_{1e} & 0 & -k_{e0} \end{bmatrix}.$$

According to Bastin and Provost (2002) it is possible to stabilise the total mass of the system $M(t) = x_1(t) + x_2(t) + x_3(t)$ at a given set-point $M^* > 0$ using the following control law:

$$u(t) = \max(0, \tilde{u}(t)) \tag{3}$$

$$\begin{aligned} \tilde{u}(t) &= k_{10}x_1(t) + k_{20}x_2(t) + k_{e0}x_3(t) \\ &\quad + \lambda(M^* - M(t)) \\ &= \underbrace{\begin{bmatrix} k_{10} & k_{20} & k_{e0} \end{bmatrix}}_{K} X(t) + \lambda(M^* - M(t)) \end{aligned} \tag{4}$$

where λ is an arbitrary design parameter.

Definition 1. The set $\Omega_{M^*} = \{X(t) : M(t) = x_1(t)+x_2(t)+x_3(t) = M^*\}$ is called an "iso-mass".

The following theorem is a slight modification of a theorem in Bastin and Provost (2002).

Theorem 1. For the closed-loop system (2)-(4) with arbitrary initial conditions $X(0) \geq 0$:

(1) the iso-mass Ω_{M^*} is forward invariant
(2) the state $X(t)$ is bounded for all $t > 0$ and converges to the iso-mass Ω_{M^*}.

Proof: See Bastin and Provost (2002).

The objective here is to track a constant reference (y_{ref}) by leading the system state to an equilibrium point $X^e = (x_1^e, x_2^e, x_3^e)$ with $x_3^e = y_{ref}$. In the sequel it is shown that the control law (3)-(4) achieves this goal. Note that if $M(t) = M^*$ (i.e. if $X(t)$ is in the iso-mass set Ω_{M^*}) then $u(t) = KX(t) \geq 0$ and the closed-loop system can be written as

$$\begin{cases} \dot{X}(t) = \tilde{A}X(t) \\ y(t) = CX(t) \end{cases} \tag{5}$$

with $\tilde{A} = A + \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}' K$.

Proposition 1. For $M(t) = M^*$, the system (5) has an equilibrium point X^e such that

$$X^e = (\alpha_1 x_3^e, \alpha_2 x_3^e, x_3^e)$$

with

$$\alpha_1 = \frac{k_{e0}}{k_{1e}}, \quad \alpha_2 = \frac{k_{12}k_{e0}}{k_{1e}(k_{21}+k_{20})},$$
$$x_3^e = \frac{M^*}{1+\alpha_1+\alpha_2}.$$

Proposition 2. Let

$$M^* = (\alpha_1 + \alpha_2 + 1)y_{ref}. \tag{6}$$

The application of the control law (3)-(4) to the system $\Sigma = (A, B, C)$ leads to $y^e = y_{ref}$.

Proof: According to Bastin and Provost (2002) the application of the control law (3)-(4) makes the closed-loop system trajectory $X(t)$ converge to the iso-mass Ω_{M^*}. This implies that for t large enough $M(t)$ is close to M^* and consequently the assumptions on k_{10}, k_{20}, k_{e0} allow to conclude that $\tilde{u}(t) = KX(t) + \lambda(M^* - M(t))$ is positive. In this case $u(t) = \tilde{u}(t)$ and the state trajectory of the corresponding closed-loop system can be decomposed as

$$X(t) = X_\Omega(t) + \Delta X(t)$$

where $X_\Omega(t)$ is a trajectory with initial condition $X_\Omega(t^*) \in \Omega_{M^*}$ corresponding to the control law

$$u_\Omega(t) = KX_\Omega(t).$$

As mentioned in Bastin and Provost (2002), Ω_{M^*} is forward invariant with this control law, and therefore $X_\Omega(t) \in \Omega_{M^*}$, for $t \geq t^*$. Moreover, it is possible to show that

$$\Delta\dot{X}(t) = \hat{A}X(t)$$

where $\hat{A} = A + BK - B\lambda[1 \quad 1 \quad 1]$ is a stable matrix. Thus

$$\lim_{t\to\infty} X(t) = \lim_{t\to\infty} X_\Omega(t)$$

Finally it can be shown that

$$\lim_{t\to\infty} X_\Omega(t) = X^e,$$

and hence $y(t) \to y_{ref}$. □

Remark 1. The control law (4) with M^* given by (6) is equivalent to a state feedback controller with reference input (Franklin *et al.*, 1991),

$$u(t) = -K_1 X(t) + (Nu + K_1 Nx)y_{ref}$$

where $K_1 = [-k_{10} + \lambda \quad -k_{20} + \lambda \quad -k_{e0} + \lambda]$ and

$$\begin{bmatrix} Nx \\ Nu \end{bmatrix} = \begin{bmatrix} A & B \\ C & D \end{bmatrix}^{-1} \begin{bmatrix} 0 \\ 1 \end{bmatrix}.$$

3. SIMULATION EXAMPLES

In this section a simulation example is presented in which the control law introduced previously is used in the control of neuromuscular blockade problem (Mendonça and Lago, 1998). To achieve a high level of muscle relaxation (neuromuscular blockade) in a short time, a *bolus* of *atracurium* is always administered in the beginning of a surgery. Following the administration of the *bolus*, the level of the muscular blockade decreases very quickly, and full muscle paralysis is induced in a few minutes. Following that initial period, the control objective is to follow a constant reference ref. For simulation purposes, a bank of $N = 100$ non-linear dynamic models, M_j, $j = 1, ..., N$, has been generated using a multidimensional log-normal probability distribution (Lago *et al.*, 1998). The relation between the effect concentration $y(t)$ $[\mu g m l^{-1}]$ and the neuromuscular blockade level $r(t)$ [%] is given by the Hill equation (Mendonça and Lago, 1998):

$$r(t) = \frac{100C_{50}^\gamma}{y(t)^\gamma + C_{50}^\gamma} \tag{7}$$

where C_{50} and γ are patient-dependent parameters. In order to obtain a set-point $r(t) = ref$, the corresponding effect concentration y_{ref} is given by

$$y_{ref} = C_{50}\left(\frac{100}{ref} - 1\right)^{1/\gamma}. \tag{8}$$

Figure 2 shows the results obtained for a simulation model from the bank assuming $ref = 10$. As can be seen, the tracking of the reference is very good.

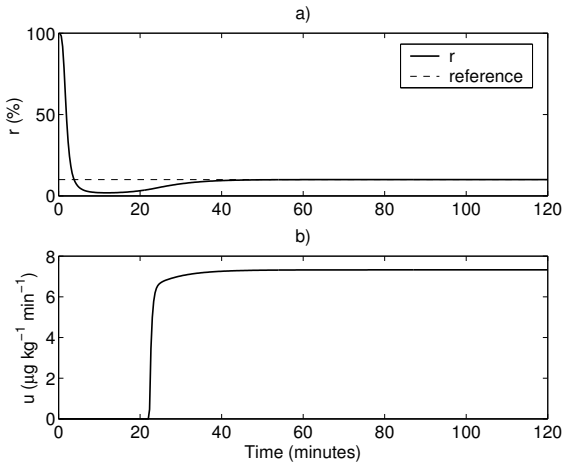

Fig. 2. Simulated neuromuscular blockade response r [%] induced by a *bolus* of 500 μgkg^{-1} of *atracurium* and the tracking reference - a). Infusion rate u $[\mu gkg^{-1}min^{-1}]$ during the period of feedback automatic control ($t > 10$ *minutes*) -b).

4. PRACTICAL IMPLEMENTATION OF THE COMPARTMENTAL CONTROL LAW

It is clear that in order to implement this control law in a clinical environment it is necessary to know the micro-rate constants described before $(k_{12}, k_{21}, k_{10}, k_{20}, k_{1e}, k_{e0})$. According to Godfrey (1983), to identify the model the Laplace transform is applied to the state-space model $\Sigma = (A, B, C)$ and the following transfer function is obtained:

$$G(s) = C(sI - A)^{-1}B = \frac{a_{31}(s - a_{22})}{\Delta(s)}$$

where $\Delta(s) = s^3 - (a_{11} + a_{22} + a_{33})s^2 + (a_{11}a_{22} + a_{11}a_{33} + a_{22}a_{33} - a_{21}a_{12})s + a_{21}a_{12}a_{33} - a_{11}a_{22}a_{33}$ and

$$\begin{aligned} a_{11} &= -(k_{10} + k_{12} + k_{1e}) \\ a_{12} &= k_{21} \\ a_{21} &= k_{12} \\ a_{22} &= -(k_{21} + k_{20}) \\ a_{31} &= k_{1e} \\ a_{33} &= -k_{e0} \end{aligned}$$

The impulsive response of such a system may be represented in terms of a disposition polyexponential $h(t)$ fitted to the effect concentration $y(t)$ given by:

$$h(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + A_3 e^{-\lambda_3 t} \qquad (9)$$

Applying the Laplace transform to (9) and after a few straightaway calculations, the following expressions for the micro-rate constants, assuming prior knowledge (*e.g.* $k_{20} = 0$) (Godfrey, 1983), are obtained:

$$\begin{aligned} k_{e0} &= \lambda_3 \\ k_{1e} &= A_1(\lambda_2 + \lambda_3) + A_2(\lambda_1 + \lambda_3) + A_3(\lambda_1 + \lambda_2) \\ k_{21} &= \left(A_1\lambda_2\lambda_3 + A_2\lambda_1\lambda_3 + A_3\lambda_1\lambda_2\right)/k_{1e} \qquad (10) \\ k_{10} &= \lambda_1\lambda_2/k_{21} - k_{1e} \\ k_{12} &= \lambda_1 + \lambda_2 - (k_{10} + k_{1e}) - \lambda_1\lambda_2/(k_{10} + k_{1e}) \end{aligned}$$

To identify the unknown parameters of the equation (9), an identification algorithm based on a nonlinear least-squares regression method using Levenberg-Marquardt (Marquardt, 1963) as a numerical optimization technique is applied (Amisaki, 1999). An identification test was done for all the models in the bank using data from the impulse response to a *bolus* dose of 500 μgkg^{-1}. Attending to the specific characteristics of the problem to be solved, the data suitable for the identification algorithm are the measured effect concentrations corresponding to the elapsed time between $t = 0$ *minutes* and the instant at which the concentration reaches a predefined threshold value $y*$. It was observed that parameter identification results strongly depend on the initial estimates. In order to overcome this drawback, the parameters of the nearest model in the sense of the Mahalanobis distance (Mendonça *et al.*, 2002) are used. Figure 3 shows the scatterplot of $\theta = (\theta_1, \ldots, \theta_6) = (A_1, A_2, A_3, \lambda_1, \lambda_2, \lambda_3)$ *versus* the estimated values $\hat{\theta}$ for all the models in the bank.

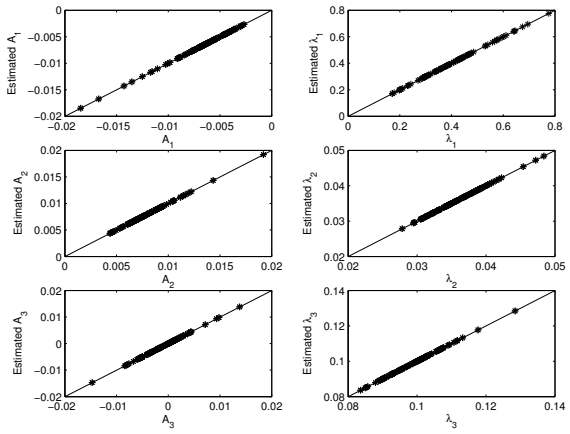

Fig. 3. Scatterplot of $\theta = (A_1, A_2, A_3, \lambda_1, \lambda_2, \lambda_3)$ *versus* the estimated values $\hat{\theta}$.

One hundred simulated neuromuscular blockade responses induced by a *bolus* of 500 μgkg^{-1} using the positive control law with the estimated micro-rate constants (10) obtained from $\hat{\theta}$ are shown in Figure 4. The parameters of the Hill equation (7), C_{50} and γ are assumed to be known. During the period of automatic control the reference is perfectly tracked for the great majority of the models (99). It is possible to adjust the λ param-

eter in (4) to completely eliminate the overshoot ($r(t) \approx 27.5\%$) presented in one of the models.

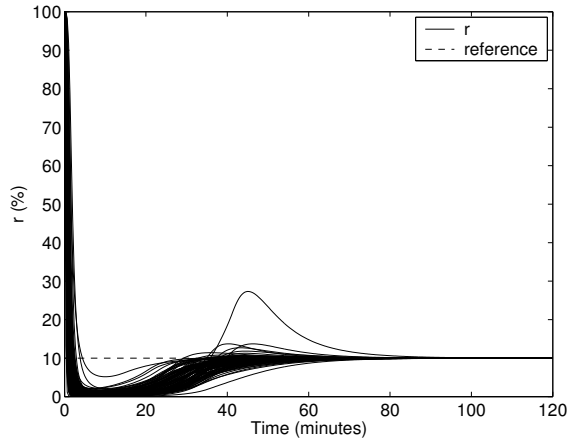

Fig. 4. One hundred simulated neuromuscular blockade responses induced by a *bolus* of 500 $\mu g k g^{-1}$ using the positive control law with the estimated micro-rate constants (10) obtained from $\hat{\theta}$.

The robustness of the estimated model parameters in the presence of noise in the measurement of the *bolus* response was investigated. Figure 5 illustrates the values of θ *versus* the estimated values $\hat{\theta}$ from the *bolus* response with added noise. To assess the performance of parameter estimation, Table 1 shows the mean, standard deviation, maximum and minimum values of the relative absolute error,

$$\sum_{k=1}^{100} \left| \frac{\theta_{ik} - \hat{\theta}_{ik}}{\theta_{ik}} \right|, \quad i = 1, \ldots, 6 \qquad (11)$$

where $\hat{\theta}_{ik}$ is the estimate of parameter θ_i obtained with model k and θ_{ik} the corresponding true value. An extensive simulation study showed that the performance of the controller strongly depends on the quality of the parameter estimates.

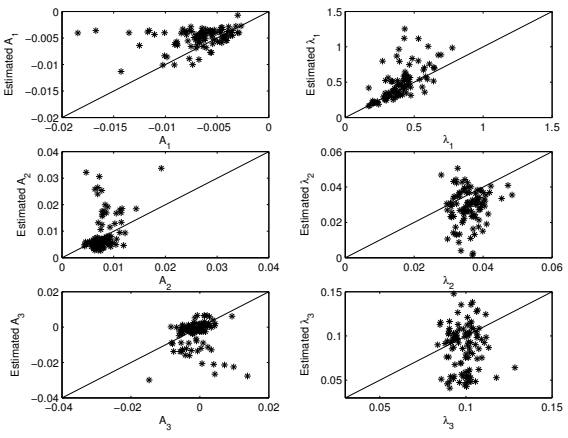

Fig. 5. Scatterplot of θ *versus* the estimated values $\hat{\theta}$ from the *bolus* response with added noise.

To obtain better performance in the reference tracking with the estimated micro-rate constants, the control law (4) was reformulated in order to incorporate integral action. Figure 6 shows one hundred simulated neuromuscular blockade responses induced by a *bolus* of 500 $\mu g k g^{-1}$ with added noise using the control law (4) with integral action, where the estimated micro-rate constants (10) are obtained from $\hat{\theta}$. The parameters of the Hill equation (7), C_{50} and γ are again assumed to be known. This assumption is not critical since in a real situation, the linear process characteristics of the neuromuscular blockade measurement are well approximated with the inversion of the non-linear Hill equation (7), using e.g. mean pharmacodynamic parameters.

Table 1. Mean, standard deviation, maximum and minimum values of the relative absolute error (11).

	Mean	Std. Dev.	Max.	Min.
A_1	0.304	0.182	0.784	0.006
λ_1	0.299	0.402	1.947	0.001
A_2	0.539	0.810	5.887	0.000
λ_2	0.272	0.215	0.959	0.000
A_3	3.668	7.650	52.167	0.004
λ_3	0.231	0.179	0.588	0.002

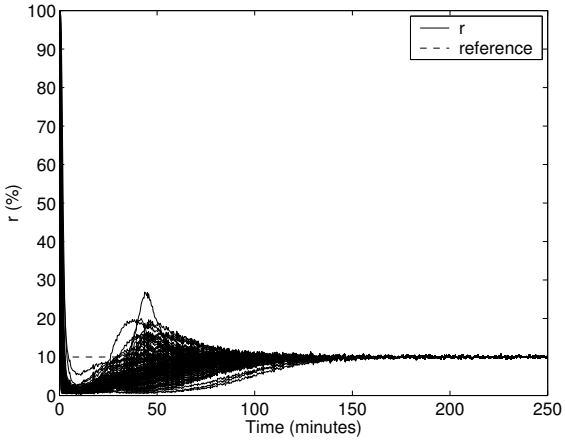

Fig. 6. One hundred simulated neuromuscular blockade responses induced by a *bolus* of 500 $\mu g k g^{-1}$ with added noise using the control law (4) with integral action, where the estimated micro-rate constants (10) are obtained from $\hat{\theta}$.

As can be seen in Figure 6, despite the initial overshoot presented in some of the models, the reference tracking is very good.

5. CONCLUSIONS

A compartmental model approach to the control of neuromuscular blockade in patients under general anaesthesia was considered. A positive control law for the feedback stabilization of the compartmental system was presented. The features of this system allowed to prove that the application of

the control law leads the system not only to a mass balance but also to a state of equilibrium, thus enabling the tracking of a constant reference. An on-line adaptive identification method based on a non-linear least squares regression strategy embedded on the positive control law was proposed and analysed. An extensive simulation study showed that the performance of the controller strongly depends on the quality of the parameter estimates. Nevertheless a superior performance of the reference tracking in the presence of noise was obtained by incorporating integral action in the positive control law.

ACKNOWLEDGEMENTS

The first author would like to thank the Foundation for Science and Technology under the Third Community Support Framework for the financial support during the course of this project.

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