NMB target level tracking via an optimization based control law

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Abstract: In this paper a state-feedback law for the control of the neuromuscular blockade level is presented. The control law is designed based on an optimal problem that is relaxed into a semi-definite program using a change of variable. For that purpose a parsimoniously parameterized model is used to describe the patient's response to a muscle relaxant. Due to clinical restrictions the controller action begins when the patient recovers after an initial drug *bolus*. The results obtained encourage the implementation of this controller in the clinical environment even in the presence of noise.

Keywords: Optimal control theory, general anesthesia, neuromuscular blockade level.

1. INTRODUCTION

Over the last years, control systems, and, in particular, feedback control, have gained increasing importance in biomedical applications. Feedback control systems use information from measurements in order to determine a suitable input signal that achieves a desired goal. Such systems have been applied to the automatic administration of anesthetics during surgeries. In this case standard physiological-based models are, in general, used to describe the relationship between the administered anesthetic dose and a measure of the corresponding effect. The effect of muscle relaxants, *e.g.*, *atracurium* or *rocuronium*, used to facilitate the intubation and other surgical procedures is measured by the neuromuscular blockade (NMB) level. This level is measured using a supra-maximal train-of-four (TOF) stimulation of the *adductor pollicis* muscle of the hand and is registered by electromyography (EEG), mechanomyography (MMG) or acceleromyography (AMG) C.McGranth and J.Hunter (2006). The NMB level then corresponds to the first response calibrated by a reference twitch and varies between 100% (full muscle activity) and 0% (full paralysis). For the great majority of clinical procedures an NMB level of 10% is desired.
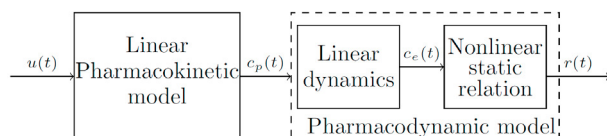

Fig. 1. PK/PD model diagram scheme.

In mathematical terms, the NMB level can be modeled by a pharmacokinetic/pharmacodynamic (PK/PD) model.
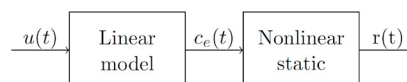

Fig. 2. PP model diagram scheme.

This is physiological model that explains the drug interactions as illustrated in Fig. 1. The first block of Fig. 1 corresponds to the pharmacokinetics, that describes how the body "absorbs" a specific drug through the different body compartments. The drug dose $u(t)$ is related with the blood concentration $c_p(t)$ by linear dynamic equations. Then, in the second block, the drug blood concentration is related with the effect concentration $c_e(t)$ by another linear dynamic equation and the measured effect $r(t)$ is obtained from $c_e(t)$ by a nonlinear static equation, known as the Hill's equation, B.Weatherley et al. (1983). This constitutes the pharmacodynamic part of the model, that studies the action of the drug on the body. This model for the NMB level was proposed in B.Weatherley et al. (1983) and involves a total of eight patient-dependent parameters.

Recently, an alternative model for the NMB response to muscle relaxants has been introduced in M.M.Silva et al. (2012) which has the advantage of involving a lower number of patient dependent parameters while keeping a good modeling accuracy, M.M.Silva et al. (2014a). For this reason this model is known as parsimoniously parameterized (PP), M.M.Silva et al. (2012). The PP model is not a physiological model and does not have a PK/PD structure. However it maintains a Wiener structure with the Hill's equation as nonlinear part, Fig. 2. Due to its advantages, the PP model has already been used for the construction of some automatic control schemes, namely one based on the control of the total drug mass J.Almeida et al. (2011),

and another using an adaptive strategy M.M.Silva et al. (2014b).

In this paper the problem of tracking the desired NMB target level of 10% is formulated as an optimal control problem (OCP). This OCP is relaxed into a semi-definite program (SDP) by replacing the original variables by their moments up to a certain order in the same line of what is done in J.Lasserre (2009). The optimal values of the moments are approximated by semidefinite programming solvers J.F.Sturm (2013), J.Lofberg (2013) and the gains of the state-feedback control law are computed based on these values. The advantage of this approach is the facility to handle state and input constraints. A comparison with other existing methods to solve OCPs with input and state constraints (such as, for instance, Pontyagruin's minimum principle) is the subject of current investigation.

According to the performed simulations, the obtained results in this way prove to be better than the ones obtained by means of a linear quadratic regulator (LQR), R.Bellman (1954).

This paper is organized as follows. Section 2 presents the NMB model used to design the control law and to simulate the patient's response. Section 3 is dedicated to the design of the state-feedback control law, and Section 4 presents the main simulation results. Finally, the conclusions are presented in Section 5.

2. NEUROMUSCULAR BLOCKADE MODEL

This section presents in more detail the PP model for the NMB level that is used to design the proposed state-feedback control law as well as to simulate the patient's response during a general anesthesia. As mentioned before, this model was introduced in M.M.Silva et al. (2012) and is composed of a linear block followed by a nonlinear block.

2.1 Linear block

The linear part of the PP model is a 3-rd order model that relates the input signal with the effect concentration thus grouping the pharmacokinetic process with the linear part of the pharmacodynamic process. This model can be represented in state-space form J.Almeida et al. (2011), as follows:

$$\dot{x}(t) = \begin{bmatrix} -l_3\alpha & 0 & 0 \\ l_2\alpha & -l_2\alpha & 0 \\ 0 & l_1\alpha & -l_1\alpha \end{bmatrix} x(t) + \begin{bmatrix} l_3\alpha \\ 0 \\ 0 \end{bmatrix} u(t) ,$$

$$c_e(t) = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} x(t) \tag{1}$$

where $x(t) = [x_1(t)\ x_2(t)\ x_3(t)]^T$ is the state vector, $u(t)$ is the administered muscle relaxant dose, $c_e(t)$ is the effect concentration and α is a patient dependent parameter. The positive parameters l_1, l_2 and l_3 only depend on the specific drug used to achieve muscle relaxation.

2.2 Nonlinear block

The relationship between the effect oncentration and the NMB level is described by a static nonlinear equation known as Hill's equation B.Weatherley et al. (1983), more concretely,

$$r(t) = \frac{100}{1 + \left(\frac{c_e(t)}{C_{50}}\right)^\gamma} , \tag{2}$$

where $r(t)$ is the NMB level and C_{50} is the half maximal effect concentration. The value of the C_{50} is kept constant for all patients according to the study performed in H.Alonso et al. (2008), whereas γ, the model parameter associated to the nonlinearity, is patient dependent.

3. FEEDBACK GAIN DESIGN

This section presents a method to design a state-feedback gain matrix for the administration of a muscle relaxant with the aim of tracking a desired NMB level. The idea is to associate the tracking problem with an optimal control problem (OCP). The OCP is relaxed into a SDP by introducing as new variables the moments of the original variables (up to a suitable order) J.Lasserre (2009). The solver SeDuMi J.F.Sturm (2013) is used here to solve the SDP numerically and the result is interfaced by means of YALMIP J.Lofberg (2013). Before considering the neuromuscular blockade level tracking problem, a general overview of the transformation of a polynomial OCP into a SDP together with the explanation of how to obtain the optimal control in the form of a feedback law is presented.

3.1 Optimal control reformulation

Consider the following optimal control problem,

$$\min_{u(t),T} \quad H(x,u) = \int_0^T h(x(t),u(t))\, dt$$
$$\text{s.t.} \quad \dot{x}(t) = f(x(t),u(t))$$
$$x(0) = x_0$$
$$x(T) = x_T \qquad\qquad , \tag{3}$$
$$(x(t),u(t)) \in \mathcal{G}$$

where $x(t) \in \mathbb{R}^n$ is the state vector, $u \in \mathbb{R}$ is the input signal, $h(x(t),u(t))$ and $f(x(t),u(t))$ are polynomial functions and $\mathcal{G}$ is the constrained region for the state and input values. This is a compact and semi-algebraic set defined as:

$$\mathcal{G} = \{(x(t),u(t)) : g_i(x(t),u(t)) \geq 0,\ \forall t \geq 0,\ i = 1,\dots,p\} \tag{4}$$
$$\subset \mathbb{R}^n \times \mathbb{R} ,$$

where each $g_i(x(t),u(t))$ is a polynomial function. In order to transform the OCP into a SDP a change of variables is made. For this purpose the new variables are defined as the moments of $\bar{x}$, *i.e.*,

$$y_\beta = \int_0^T \bar{x}^\beta\, dt , \tag{5}$$

where $\beta = (\beta_1,\dots,\beta_n,\beta_{n+1})$ is a multi-index, $\bar{x}(t) = (x(t),u(t)) \in \mathbb{R}^{n+1}$ and $\bar{x}^\beta = \prod \bar{x}_i^{\beta_i}$.

Similar to what is done in J.Lasserre (2009), a linear functional L on the polynomial functions in $(n+1)$ variables is introduced in the following way. Given $p(\bar{x}) = \sum_{\beta \in \mathbb{N}^{n+1}} p_\beta\, \bar{x}^\beta$, L is defined as:

$$L(p) = \sum_{\beta \in \mathbb{N}^{n+1}} p_\beta\, y_\beta . \tag{6}$$

This amounts to replacing the monomials in p by the corresponding integrals, according to (5). Based on the moments y_β with $\beta \in \mathcal{B}_d \overset{\text{def}}{=} \{(\beta_1,\dots,\beta_{n+1}) \in \mathbb{N}^{n+1} : \sum_{j=1}^{n+1} \beta_j \leq d\}$ one also introduces the moment matrix

of order d, $M_d(y)$, which plays an important role in the reformulation of the OCP (3). The moment matrix has rows and columns labeled by:

$$V_d(\bar{x}) = [1, \bar{x}_1, \bar{x}_2, \ldots, \bar{x}_{n+1}, \bar{x}_1^2, \bar{x}_1\bar{x}_2, \ldots \qquad (7)$$
$$\ldots, \bar{x}_1\bar{x}_{n+1}, \bar{x}_1^d, \ldots, \bar{x}_{n+1}^d]^T$$

and is constructed as follows:

$$M_d(y) = L\left(V_d(\bar{x})\,V_d(\bar{x})^T\right) \qquad (8)$$

with L as defined in (6). This means that L is applied to each entry of the matrix $V_d(\bar{x})\,V_d(\bar{x})^T$.

It is also useful to define the moment vector of order d as $y = L(V_d(\bar{x}))$.

As a consequence, the cost functional $L(x,u)$ can be rewritten as

$$L(h) = \sum_\beta h_\beta\, y_\beta \quad, \qquad (9)$$

where h_β are the coefficients of the polynomial $h\left(x(t), u(t)\right)$ in the OCP formulation (3).

To incorporate the system dynamics and the end-point constraints as constraints of the demi-definite, monomial test functions $\upsilon(x)$ will be considered. These functions are polynomial functions given by $\upsilon(x) = x^\beta$. Note that, on one hand, from the Fundamental Theorem of Calculus:

$$\int_0^T \frac{d\upsilon}{dt}\,(x(t))\,dt = \upsilon\left(x(T)\right) - \upsilon\left(x(0)\right) \quad, \qquad (10)$$

and on the other hand, using the chain rule and the system dynamics the total time derivative is equal to:

$$\frac{d\upsilon(x)}{dt} = \frac{\partial\upsilon}{\partial x} \cdot \frac{dx}{dt} = \frac{\partial\upsilon}{\partial x} \cdot f\left(x(t), u(t)\right) \quad. \qquad (11)$$

Thus for each function $\upsilon(x)$ one obtains:

$$\int_0^T \frac{\partial\upsilon}{\partial x} \cdot f\left(x(t), u(t)\right)\,dt = \upsilon(x_T) - \upsilon(x_0) \quad \forall\upsilon \quad. \qquad (12)$$

Since f is a polynomial function of x and u and υ and $\frac{\partial\upsilon}{\partial x}$ are polynomial functions of x this equation can be rewritten in terms of the moments as: $\sum_j a_{ij} y_{\alpha_j} = b_i$, where the multi-index α_j varies so as to yield all the relevant moments.

To handle the state and input constraints the localizing matrix $M_d(g_i y)$ with respect to y and to the polynomials $g_i(\bar{x}) = g_i(x(t), u(t))$ is defined. This matrix is obtained from $M_d(y)$ by:

$$M_d(g_i y) = L\left(g_i V_d(\bar{x})\,V_d(\bar{x})^T\right) \quad \forall i = 1, \ldots, p \qquad (13)$$

with $V_d(x)$ defined in (7). In this way the OCP is replaced by the following SDP: ,

$$\min_y \quad L(h)$$
$$\text{s.t.} \quad \sum_j a_j y_{\alpha_j} = b_j$$
$$M_d(y) \geq 0 \qquad (14)$$
$$M_d(g_i y) \geq 0 \quad \forall i = 1, \ldots, p$$

where p is the number of state and input constraints. This problem is solved using the solver SeDuMi J.F.Sturm (2013) and the values of the optimal moments $y_\beta = y_\beta^*$ are obtained.

<u>Remark:</u> Since the considered moment matrix has finite order d, this SDP is not equivalent to the original problem. Therefore, the solution to this problem is only on

approximation to the solution of the OCP. As $d \to \infty$ the approximation converges to the optimal solution (under some mild assumptions stated in J.Lasserre (2009)). Due to this reason, it is necessary to check if the obtained solution indeed satisfes the original contraints.

Expressing u as a state-feedback, ,

$$u(t) = u^* + \sum_{i=1}^n K_i\, x_i(t) \quad. \qquad (15)$$

with unknown gains K_i, and replacing (15) in the moments that involve u, these can be expressed in terms of other the moments. For instance, for a simple system with two state components, x_1, x_2 and one input u, the moment y_{101} becomes:

$$y_{101} = \int_0^T x_1(t)u(t)\,dt = \int_0^T x_1(t)\left(u^* + K_1 x_1(t) + K_2 x_2(t)\right)dt$$
$$= \int_0^T u^* x_1(t) + K_1 x_1^2(t) + K_2 x_1(t)x_2(t)\,dt$$
$$= u^* y_{100} + K_1 y_{200} + K_2 y_{110} \qquad (16)$$

Proceeding in the same way for the other moments yields a system of linear equations. After the values of the optimal moments are obtained and replaced in the system, the feedback gains can be computed.

3.2 Application to the NMB model

In this section the problem of tracking a reference level for the NMB is viewed as an optimal control problem and the previous method is applied with the aim of designing a suitable state-feedback control law. The idea is to achieve the target value x^e that corresponds to the steady state value associated with the desired NMB level. Since, the control objective is to achieve a target value x^e, a change of coordinates $\hat{x} = x - x^e$ is chosen to transform the original control objective into a problem of stabilization to the origin. In this way the following OCP can be formulated,

$$\min_{u(t),T} \int_0^T \hat{x}^T(t)Q\hat{x}(t) + u^T(t)Ru(t)\,dt$$
$$\text{s.t.} \quad \dot{\hat{x}}(t) = A\hat{x}(t) + b + B\,u(t)$$
$$\hat{x}(0) = \hat{x}_0 \qquad (17)$$
$$\hat{x}(T) = \hat{x}_T$$
$$(\hat{x}(t), u(t)) \in \mathcal{G} = \{(\hat{x}, u) \in \mathbb{R}^n \times \mathbb{R} : \hat{x} \geq -x^e, u \geq 0\}$$

with $Q = Q^T \geq 0$ and $R > 0$. The model (1) is rewritten using the new state vector $\hat{x}(t)$. In turn, the target value x^e is obtained by the inversion of Hill's equation (2) for a desired NMB level of 10%, and corresponds to the desired effect concentration. The matrix A and the vector B are as in the model (1) and the vector $b = -B\,u^e$ where u^e represents the steady-state input corresponding to the steady-state x^e, and can be shown to coincide with the third component x_3^e of that state; $\hat{x}_0$ and $\hat{x}_T$ are known initial and final conditions, respectively, and are known. The state-feedback control law is,

$$u(t) = u^e + K\hat{x} = x_3^e + K\hat{x} \quad, \qquad (18)$$

where K is the vector of gains. The OCP (16) is transformed into the SDP (14) with $d = 2$, since the cost functional is quadratic and the constraints are affine, and solved as described before. Note that this is not a standard Linear Quadratic Regulator (LQR) problem, since the control and the states are subject to contraints. This motivates the application of the method of moments presented in subsection 3.1.

4. SIMULATION RESULTS

In order to analyse the performance of the presented method for the feedback gain design a bank $\mathcal{R}$ of sixty models R_i with parameters (α_i, γ_i) $(i = 1, \ldots, 60)$ was used. More concretely, the case shown here corresponds to the mean of the offline identification of the sixty cases collected during general anesthesia where the muscle relaxant used was *atracurium*. For this drug the values of l_1, l_2, l_3 of the NMB model are $1, 4, 10$, respectively, according to M.M.Silva et al. (2012), $\alpha = 0.0355$ and $\gamma = 2.758$. Due to clinical restrictions the controller action begins when the patient recovers after an initial drug *bolus* of $500\mu/kg$ of *atracurium*. The point of recovery t^* is determined by the algorithm OLARD proposed in M.M.Silva et al. (2009).

The control strategy used here can be summarized by the following steps:

- First, a *bolus* of muscle relaxant of $500\mu g/kg$ is administered and the patient's response is monitored to determine the recovery time instant t^*;
- The time instant t^* is determined by the algorithm OLARD;
- After time t^* the optimal control solution is computed, the feedback are determined, and the corresponding state feedback controller is set into action.
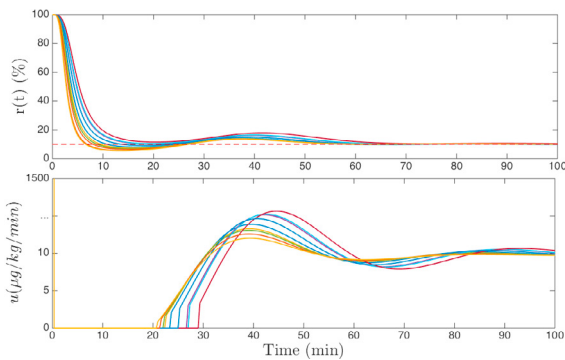

Fig. 3. Simulation of the NMB level (upper plot) using the state-feedback control (bottom plot) for ten patients.

Fig. 3 presents the NMB responses and the corresponding input doses obtained by solving the OCP (17) for ten patients. As it is possible to see although the patient parameter variability the desired target is achieved.

Fig.4 shows the simulation of the NMB level after the application of the state-feedback control law obtained by solving problem (17) with $Q = 10I$, $R = 10$ and $T = 325\,min$. In this case, the optimal moment matrix obtained by the solver SeDuMi, is given by:

$$M^* = M_2(y^*) = 10^3 \begin{bmatrix} 0.0617 & 0.2406 & 0.1526 & -0.0072 & 0.7250 \\ 0.2406 & 1.2024 & 0.8197 & -0.0874 & 2.6424 \\ 0.1526 & 0.8197 & 1.3709 & 0.6042 & 1.2575 \\ -0.0072 & -0.0874 & 0.6042 & 1.0576 & -0.4597 \\ 0.7250 & 2.6424 & 1.2575 & -0.4597 & 8.8473 \end{bmatrix}$$

and the feedback gains can be computed from the following system of linear equations:

$$\begin{bmatrix} M^*(2,5) - u^e \\ M^*(3,5) - u^e \\ M^*(4,5) - u^e \end{bmatrix} = \begin{bmatrix} M^*(2,2) & M^*(2,3) & M^*(2,4) \\ M^*(3,2) & M^*(3,3) & M^*(3,4) \\ M^*(4,2) & M^*(4,3) & M^*(4,4) \end{bmatrix} \begin{bmatrix} K_1 \\ K_2 \\ K_3 \end{bmatrix}$$

(19)

yielding,

$$\begin{bmatrix} K1 & K2 & K3 \end{bmatrix} = \begin{bmatrix} 1.1890 & -0.6249 & 0.0696 \end{bmatrix}$$

With the aim of evaluating the reference tracking performance, the relative error between the controlled NMB level and the desired level of 10% was computed. As shown in Fig. 5 this error becomes less than 5% after $45\,min$ of control action and converges to zero, which is very satisfactory from the clinical point of view. Moreover, as can be seen in Fig. 4, the control input $u(t)$ is always non-negative. It can be shown that, due to the structure of the system, this implies that also the state components $x = \hat{x} + x^e$ are non-negative. Therefore, the original problem constraints are satisfied.
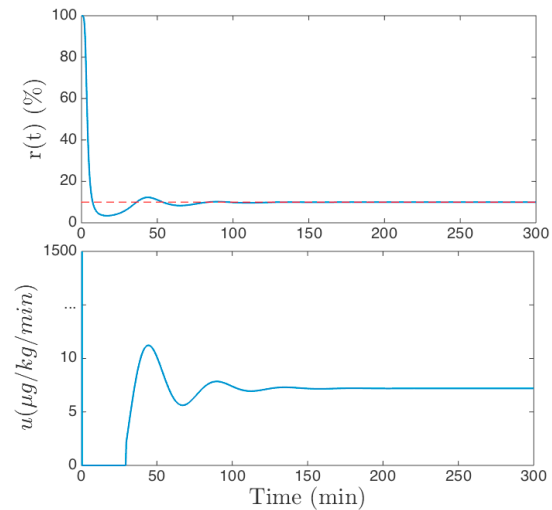

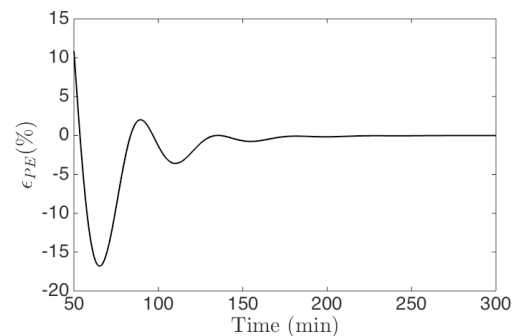Fig. 4. Simulation of the NMB level (upper plot) using the state-feedback control (bottom plot).

Fig. 5. Time-evolution of the error between the controlled NMB level and the target level of 10%, after the time instant of the recovery.

Fig. 6 shows the performance of the state-feedback control law in the presence of noise. The noise added to the simulated signal was taken from a typical NMB real record and corresponds to the residuals obtained by the application of the filter described in T.Mendonça et al. (2004). This noise vector is typically used to analyse the performance of controllers in the presence of noise, M.M.Silva et al. (2012). The control law has a good performance even in the presence of noise.
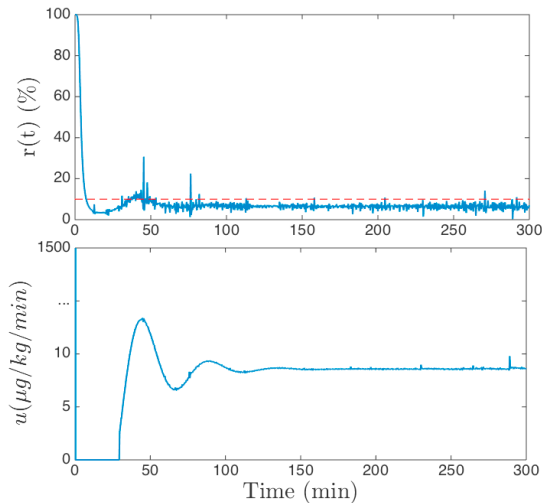
Fig. 6. Simulation of the NMB level (upper plot) using the state-feedback control law (bottom plot).

In order to compare the performance of the method presented here an alternative feedback controller is determined using a linear-quadratic regulator (LQR). For that purpose, the MATLAB command line, *lqrd* is used with the same weighting matrices as in (17). The following gain vector was obtained with the application of the LQR,

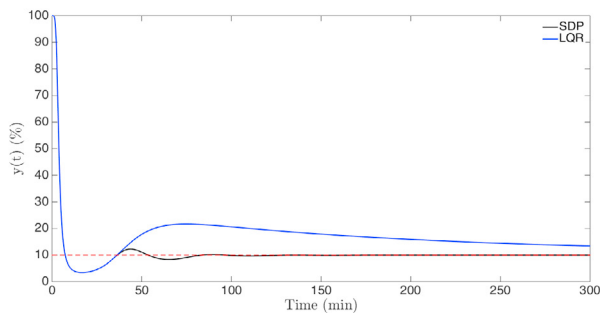$$[K1 \ K2 \ K3] = [0.4606 \ 0.2819 \ 0.2018] . \qquad (20)$$

Fig. 7. Patient's response when the control inputs are determined by the two approaches.

Fig. 7 shows the patient's response when the control inputs are determined by the two approaches. As can be seen, the control input obtained by solving problem (17) presents a superior performance and achieves a better reference tracking than the control input given by the solution of the LQR.

5. CONCLUSION

In this paper a state-feedback law was designed to control the neuromuscular blockade level in the scope of general anesthesia. To obtain the control law, an optimal control problem was formulated and relaxed into a semi-definite program by the method of moments. The feedback gains were computed from the optimal moments obtained by the solver SeDuMi. A comparison of this method with a standard LQR was performed, showing that the former has a better performance than the latter. The next step is to apply this approach in clinical environment during a general anesthesia.

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