Computer Implementation of Robust Controllers for Anesthesia*

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Abstract. The reversible state of a general anesthesia encompasses three components: hypnosis, paralysis and analgesia. In this paper design and implementation issues of the controllers used to maintain paralysis and hypnosis are presented. The controllers are designed from model databases of compartmental models and rely on the H_∞ method. In order to cope with the variability of the patient models, robust techniques are used to produce a controller that is able to withstand robust stability and robust performance. The controllers are designed in continuous and discretized for computer implementation. Clinical results during elective surgery are presented to illustrate the results obtained.

Keywords: Robust control; H_∞ design; Depth of anesthesia; Neuromuscular blockade; Clinical trials

1 Introduction

Closed-loop control of anesthesia has been the subject of several previous studies, either to identify models of the patient's response to drug infusion, or to design controllers based on several methodologies in order to achieve a proper anesthetic state. Like any other drug induced state, performing anesthesia is not a straightforward process, because the effect of a certain drug dose differs not only from patient to patient but over time of exposure to the drug. Nevertheless, the patient's response may be related to features such as age, weight, height, gender and ethnicity, that can be used to infer the most suitable dosage. The anesthetists use these informations to perform drug dosing and, as the surgery proceeds, they close the loop by adjusting the dosage relying on their experience. However, an automatic closed-loop mechanism, with the appropriate measured variables, can be a breakthrough in this medical process.

The reversible state of anesthesia comprehends three effects: hypnosis, paralysis and analgesia. In a general anesthesia, hypnosis or depth of anesthesia (DoA)

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is induced by the hypnotic drugs that act on the synaptic transmission on the neuronal network, enabling the loss of consciousness during the surgical intervention. Several models of the hypnotic effect on patients have been described in [1–3], in particular for the effect of the drug *propofol*. Other studies identified the interaction of the analgesic drug *remifentanil* with the hypnotic effect, measured by the BIS index [4]. The BIS index is a processed data from the patient's electroencephalogram that can be related to the hypnotic state of the patient. The BIS index is a value between 0 and 100 that measures the "awareness" of the patient, being 100 for full awareness. During surgery, the BIS index is usually kept close to 50.

The effect of paralysis is achieved with muscle relaxant drugs that act on the neuromuscular junction between the neuron and the muscle fiber. This effect is also called the neuromuscular blockade (NMB) since the drugs, like *rocuronium*, block the neuromuscular signal transmission, inhibiting muscle contraction. Similarly to hypnosis, compartmental models have also been described for paralysis [5], relating the NMB index with the drug infusion rate. In this case, the NMB index is the train-of-four (TOF) ratio that measures the muscle contraction at the thumb after an electrical stimulation of the ulnar nerve, with four twitches. The contractions are measured by the sensor placed on the hand of the patient which result in a TOF ratio between 100 % and 0 %. During the induction of NMB the index drops from 100 %, that corresponds to no blockade, to (near) 0 %, where the paralysis is achieved. During the surgery, the NMB index is usually maintained near 10 % and should not be over 20 % to avoid muscle contractions that may interfere with the surgery procedure.

Control algorithms have been described for NMB and hypnosis, such as PID [6, 7] or adaptive controllers [8–10]. However, the robust approach to overcome uncertainty of the patient models, with the NMB index TOF ratio and the BIS index, is seldom in the literature. The uncertainty on these systems is very high, mostly due to the variability of the patient responses. The unmodelled dynamics and the errors introduced by the linear approximation of the nonlinear term of these Wiener structure models are also sources of uncertainty. The design of a controller that takes these uncertainties into account can be a great improvement on the automatic control of anesthesia, since the controllers are designed with the ability to stabilize a large group of patients and with appropriate control actions that provide appropriate clinical responses.

This paper presents two controllers, one for NMB and another for hypnosis, with the BIS index, that are designed based on the H_∞ methods. With the H_∞ approach, the loop shaping of the sensitivity and of the complementary sensitivity functions allow the desired performance and robust requirements to be fulfilled. The controllers are designed in continuous and then discretized for computer implementation. The contribution of the paper consists on the comparison of a reduced order controller that operates in discrete time and its assessment on clinical trial.

This paper is organized as follows: the control design based on H_∞ methods is briefly explained in section 2; the resulting controllers are set in the operating

room during elective surgery and results are presented in section 3; conclusions are drawn in section 4.

2 Controller Design

The control design is performed based on the patient models described in Appendix. The nonlinear models are linearized around equilibrium values of 10 % for NMB index and 50 for BIS index. The corresponding incremental models are described in continuous time by a function $G(s)$, with the patient response being

$$y(s) = G(s)\ u(s), \tag{1}$$

where u is the drug infusion rate, s is the Laplace variable and y the increment of either BIS or NMB..

For the robust control design approach that is followed in the design of the controllers for NMB and for hypnosis, a database of models is considered for each one of the problems. The controller is designed for a nominal model and based on the uncertainty that is present in the model database. For the control of NMB a database of 50 models defined as $\mathcal{G}_{\mathcal{NMB}} = \{G_i(s), i = 1, 2, ..., 50\}$ is considered, whereas the control of hypnosis considers a database of 18 models defined as $\mathcal{G}_{\mathcal{DOA}} = \{G_i(s), i = 1, 2, ..., 18\}$. For each of the databases, the multiplicative uncertainty is denoted as $\Delta_i(j\omega)$, for frequency ω, by which each model G_i is related to the nominal model G_N by

$$G_i(j\omega) = G_N(j\omega)(1 + \Delta_i(j\omega)). \tag{2}$$

2.1 Robust stability condition

To design a robust controller K it is taken into account that the controller must be able to stabilize not only the nominal model, for which it is designed, but also the models of the class considered.

Defining an upper bound $l(\omega)$ for the uncertainty Δ_i

$$|\Delta_i(j\omega)| < l(\omega), \tag{3}$$

the robust stability condition can be written as

$$\frac{1}{l(\omega)} < |T_N(j\omega)|, \tag{4}$$

where T_N is the complementary sensitivity function defined by

$$T_N(j\omega) \triangleq \frac{KG_N(j\omega)}{1 + KG_N(j\omega)}. \tag{5}$$

Accordingly, the controller that yields condition (4), taking (3) into account, has robust stability. In this design, both controllers fulfill this requirement (data not shown).

2.2 Robust performance conditions

To design the controller for robust performance, loop-shaping methods are applied to the system, while assuring that the robust stability condition is fulfilled. For that sake, in order to design a controller K, interconnected with the plant as in Fig. 1, two weighting functions W_S and W_T are coupled to the system. The

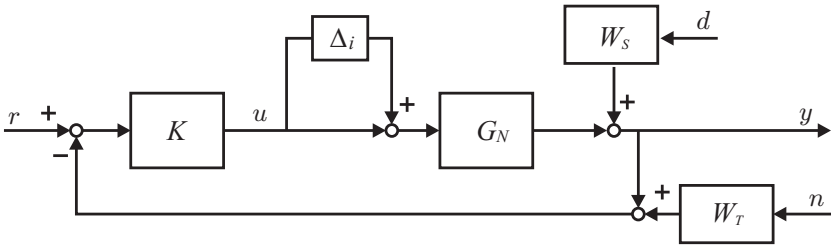

Fig. 1. Schematic representation of the control design system with use of the two weighting functions W_S and W_T and with the representation of the multiplicative uncertainty Δ_i of each model G_i with respect to the nominal model G_N; the resulting controller K filters the error between the reference r and the output y that is affected by output disturbances d and sensor noise n

closed-loop response y is described then by

$$y = \frac{W_S}{1 + KG_i}\, d + \frac{KG_i}{1 + KG_i}\, r + W_T \frac{KG_i}{1 + KG_i}\, n, \tag{6}$$

and the control problem is to minimize the weighted sensitivity functions and the weighted complementary sensitivity functions such that,

$$|S_i\ W_S| < 1 \qquad \Leftrightarrow \qquad |S_i| < \frac{1}{|W_S|}, \tag{7}$$

and

$$|T_i\ W_T| < 1 \qquad \Leftrightarrow \qquad |T_i| < \frac{1}{|W_T|}. \tag{8}$$

Therefore, the inverse of the weighting functions W_S and W_T are selected as upper bounds of the sensitivity functions S_i and of the complementary sensitivity functions T_i, respectively.

The condition (7), with a high-pass stable function W_S^{-1} that bounds the low frequency range, assures that the output disturbance d is rejected and does not cause significant deviations since the gain of S_i is less than 1 (or 0 dB). On the other hand, the condition (8), with a low-pass stable function W_T^{-1} that bounds the high frequency range, guarantees that the high frequency sensor noise is also rejected since it shapes the functions T_i to have a gain less than 1. The conditions (7) and (8) are imposed for the control design along with the robust stability condition (4) and this is accomplished with the choice of the two weighting functions, shown in Fig. 2 for the controller of hypnosis (data not shown for the controller of NMB for lack of space).

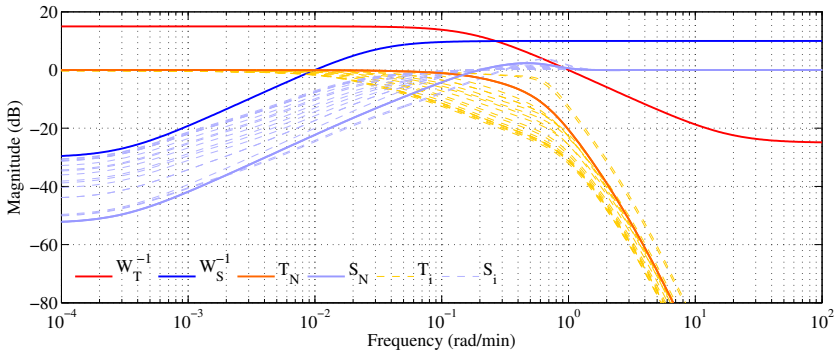

Fig. 2. Magnitude of the inverse of the weighting functions, W_S^{-1} and W_T^{-1}, and of the sensitivity functions S_i and of the complementary sensitivity functions T_i, for all models of the database $\mathcal{G}_{\mathcal{DOA}}$

The implementation of the design method is performed with the available software of MATLAB® Robust Control Toolbox™[11]. To avoid tracking errors integral action is forced in the controller. For appropriate implementation of the software used, the integrator is coupled with the model and, afterwards, it is coupled to the controller. The resulting controllers, before being enlarged with the integrator, are state-space systems of order 17 and 19 for NMB and hypnosis, respectively. These controllers are then approximated by systems of order 4 and 7, respectively, by using the method balanced truncation model order reduction implemented in the MATLAB® function `reduce` of the Robust Control Toolbox™. The frequency response of the complementary sensitivity and sensitivity functions of the nominal systems with the full order and with the reduced order controller are shown for comparison in Fig. 3 for hypnosis, and in Fig. 4 for NMB.

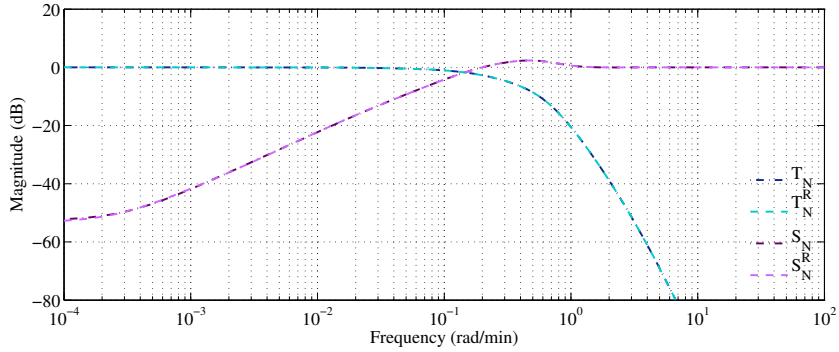

Fig. 3. Comparison between the full order and the reduced order controller for hypnosis: frequency response of the sensitivity functions of the nominal model, S_N and S_N^R respectively, and of the complementary sensitivity functions, T_N and T_N^R respectively

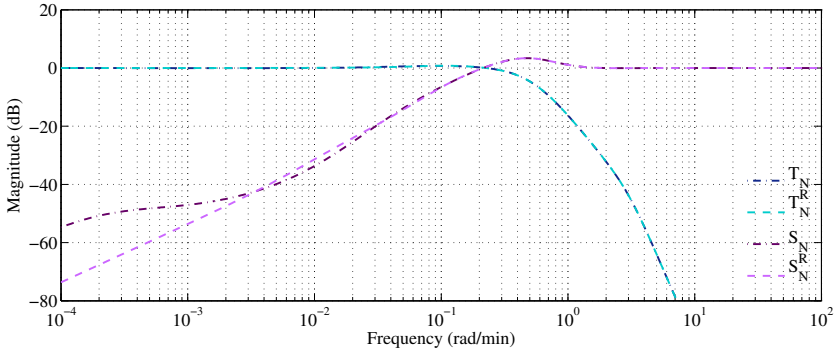

Fig. 4. Comparison between the full order and the reduced order controller for NMB: frequency response of the sensitivity functions of the nominal model, S_N and S_N^R respectively, and of the complementary sensitivity functions, T_N and T_N^R respectively

Since the controllers are designed in the continuous time domain, for computer implementation the controllers must be discretized. In this case, the controllers are discretized with the same sampling interval that the output is measured, which corresponds to 20 seconds for the controller of NMB and 5 seconds for the controller of hypnosis, and is performed with the ZOH method.

For the reduced complexity controllers in the discrete time domain, robust stability and robust performance conditions are checked. For both controllers, the robust stability condition is satisfied. The verification of the performance conditions is shown in Fig. 5 for the controller of hypnosis, in the discrete time domain. However, for the NMB controller not all the complementary sensitivity

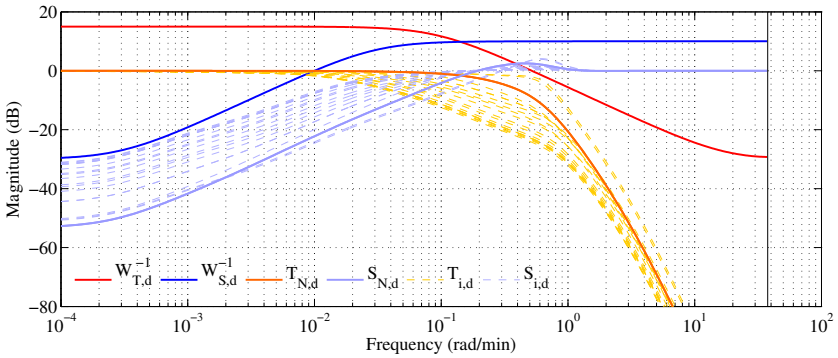

Fig. 5. Magnitude of the inverse of the weighting functions, W_S^{-1} and W_T^{-1}, and of the sensitivity functions S_i and of the complementary sensitivity functions T_i, for all models of the database $\mathcal{G}_{\mathcal{DOA}}$ in the discrete time domain

functions of $\mathcal{G}_{\mathcal{NMB}}$ fall bellow the upper bound W_T and, therefore, the noise rejection condition is not fulfilled in discrete time (data not shown). Nevertheless

the controller is able to deliver appropriate performances, with high frequency noise rejection, both in simulations and in clinical trials.

3 Clinical Trials

The controllers have been evaluated in clinical trials. Several safety measures are taken in order to guarantee the patient's safety. The controller is equipped with an override command that enables the anesthetist to switch it off and also to adjust manually the dosage if required. In this paper, a clinical trial where both controllers are used in simultaneous is reported in Fig. 6. The controllers are switched on after an initial *bolus* of the drug that drives the patient state near the required levels. No override command is used, and the controllers are able to adjust the dosage for appropriate hypnosis and paralysis levels. The controllers are able to filter the high frequency noise.

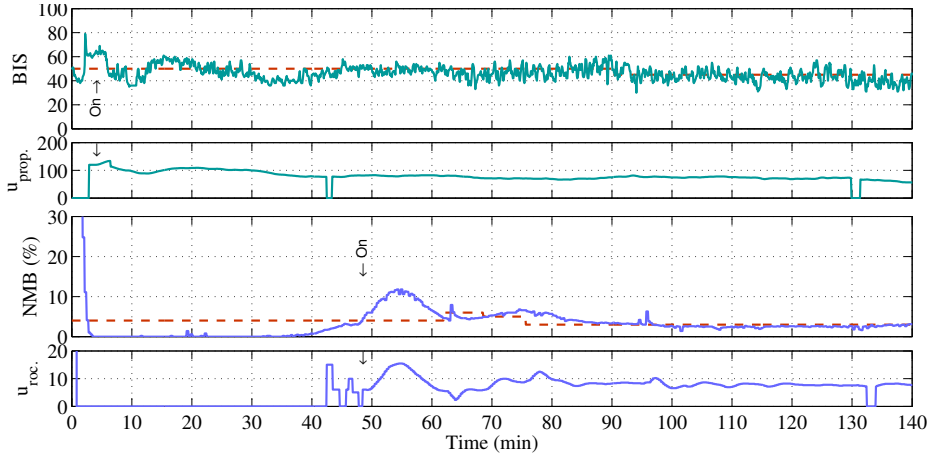

Fig. 6. Closed-loop control with the robust controllers used during a surgery in a 54 years old male patient with 76 kg and 1.76 m: the first couple plots are the BIS index measured and the drug dosage of *propofol*; the second couple plots are the NMB index measured and the drug dosage of *rocuronium*; the red dashed lines are the reference levels and the vertical arrows indicate the moment that the controllers are switched on; the first minutes of the surgery are omitted to simplify the exposition; the drug dosages are in μg.kg^{-1}.min^{-1}

4 Conclusions

In this paper two robust controllers designed for anesthesia, in order to automate the closed-loop control of hypnosis and paralysis are presented. The loop-shaping techniques applied allowed the design of robust controllers that are able to deliver adequate clinical performances. The controllers are able to stabilize the patient,

both in simulation and in clinical trials, performing high frequency sensor noise rejection and output disturbance rejection. The order reduction and the discretization allowed an appropriate computer implementation of the closed-loop system and the results show the adequacy of the controllers designed.

Appendix: Dynamic models of NMB and hypnosis

The models of the patient's response to the drug infusion considered have a Wiener structure, where a static nonlinearity appears in series with a linear model. The patient models are pharmacokinetic/pharmacodynamic (PK/PD) models described as multi-compartmental models, where the drug is assumed to be uniformly distributed in each compartment, with constant transfer rates. The compartmental models are represented in Fig. 7.

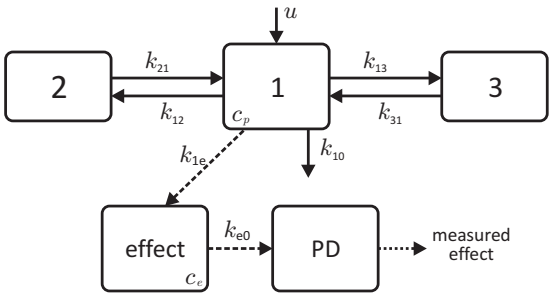

Fig. 7. Schematic representation of the patient response model: the drug u is perfused in the first compartment that is in equilibrium with two compartments; the drug concentration in plasma c_p is related with the drug concentration in the effect compartment c_e, which is related to the measured effect by the PD model; the compartment (3) is not considered in the NMB model

The linear model relates the effect concentration, which is the drug concentration that corresponds to the measured effect, with the drug infusion rate. The linear part of the patient model is described, in state-space representation, by

$$\begin{cases} \dot{\mathbf{x}}(t) = \mathbf{A}\ \mathbf{x}(t) + \mathbf{B}\ u(t) \\ c_e(t) = \mathbf{C}\ \mathbf{x}(t) \end{cases}, \tag{9}$$

where $\mathbf{x}$ and $\dot{\mathbf{x}}$ are the column vectors of the state-space variables x_i and of its derivatives, respectively. The state matrix $\mathbf{A}$ is a patient dependent matrix and matrices $\mathbf{B}$ and $\mathbf{C}$ are the input and output matrices of the system. The output of the linear system is the effect concentration c_e that is related to the measured NMB effect by a static nonlinearity modeled by the nonlinear Hill equation.

The NMB patient response model is represented by a 3-compartmental linear model (compartments (1), (2) and the effect compartment), that corresponds to the PD model, followed by the PD model described by the nonlinear Hill equation, as represented in Fig. 7. The linear part of the NMB model is described

by (9), where the state matrix $\mathbf{A}$ is

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

where k_{ij} is the constant rate from the i-th to the j-th compartment. The state is defined as $\mathbf{x} = [x_1\ x_2\ x_e]^T$, $\mathbf{B} = [1\ 0\ 0]^T$ and $\mathbf{C} = [0\ 0\ 1]$. The nonlinear Hill equation for the NMB model is defined as

$$y(t) = 100\frac{C_{50}^{\gamma}}{C_{50}^{\gamma} + c_e^{\gamma}(t)}, \tag{11}$$

where y(t) is the measured effect by the NMB index (TOF ratio), which is a value normalized between 0 % and 100 %, corresponding to full paralysis and no paralysis, respectively. The variables C_{50}, which corresponds to the effect concentration related to 50 % of the NMB index, and γ are patient dependent ones.

The hypnotic response model considered is represented by a 4-compartmental linear model, followed by the nonlinear Hill equation (Fig. 7). The linear part of the hypnotic model is described by (9), where the state matrix $\mathbf{A}$ is

$$\mathbf{A} = \begin{bmatrix} -(k_{10}+k_{12}+k_{1e}) & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ \frac{k_{1e}}{1000\ V} & 0 & 0 & -k_{e0} \end{bmatrix}, \tag{12}$$

where k_{ij} is the constant rate from the i-th to the j-th compartment and V is the volume of the first compartment, and the state is defined as $\mathbf{x} = [x_1\ x_2\ x_3\ x_e]^T$, $\mathbf{B} = [1000/60\ 0\ 0\ 0]^T$ and $\mathbf{C} = [0\ 0\ 0\ 1]$. The nonlinear part of the hypnotic model is described the Hill function described by

$$y(t) = E_0 + (E_{max} - E_0)\frac{c_e^{\gamma}(t)}{c_e^{\gamma}(t) + C_{50}^{\gamma}}, \tag{13}$$

where $y(t)$ is the BIS index that ranges between 100, when the patient is fully aware, and 0, E_0 is the baseline effect at zero drug concentrations, E_{max} is the peak drug effect, C_{50} is the concentration related with 50 % of the drug effect and γ is the steepness of the concentration-response relation. As described in [4], exists a synergetic effect between the hypnotic drug *propofol* and the analgesic drug *remifentanil*, shown in the electroencephalogram, for which the overall effect becomes described by

$$y(y) = \frac{97.7}{1 + \left((1+\beta)\,\frac{c_e^p(t)}{C_{50}^p} + \frac{c_e^r(t)}{C_{50}^r}\right)^{\gamma}}, \tag{14}$$

where β is a patient dependent parameter and the super-indexes p and r refer to the variables associated with *propofol*, and the hypnotic model, and to the variables associated with *remifentanil*, and the analgesic model, respectively. In this work, the *remifentanil* dose that appears in the model is handled as an unaccessible disturbance.

References

1. Marsh, B., White, M., Morton, N., Kenny, G.N.C.: Pharmacokinetic model driven infusion of propofol in children. British Journal of Anaesthesia **67**(1) (Jul. 1991) 41–48
2. Dyck, J.B., Shafter, S.L.: Effects of age on propofol pharmacokinetics. In: Seminars in Anesthesia. Volume 11., Implemented in the computer program Stanpump (May 1992) 2–4
3. Schnider, T.W., Minto, C.F., Shafer, S.L., Gambus, P.L., Andresen, C., Goodale, D.B., Youngs, E.J.: The influence of age on propofol pharmacodynamics. Anesthesiology **90**(6) (Jun. 1999) 1502–1516
4. Bouillon, T.W., Bruhn, J., Radulescu, L., Andresen, C., Shafer, T.J., Cohane, C., Shafter, S.L.: Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology **100**(6) (Jun. 2004) 1353–72
5. Lago, P., Mendonça, T., Gonçalves, L.: Online autocalibration of a PID controller of neuromuscular blockade. In: Proceedings of the 1998 IEEE International Conference on Control Applications. Volume 1. (Sep. 1998) 363–367
6. Macleod, A.D., Asbury, A.J., Gray, W.M., Linkens, D.A.: Automatic control of neuromuscular block with atracurium. British Journal of Anaesthesia **63** (Jul. 1989) 31–35
7. Absalom, A., Sutcliffe, N., Kenny, G.N.: Closed-loop control of anesthesia using bispectral index: performance assessment in patients undergoing major orthopedic surgery under combined general and regional anesthesia. Anesthesiology **96**(1) (Jan. 2002) 67–73
8. Struys, M., De Smet, T., Versichelen, L., Van de Vilde, S., Van der Brocke, R., Martier, E.: Comparison of closed-loop controlled administration of propofol using BIS as a controlled variable vesus standard practice controlled administration. Anesthesiology **95**(1) (2001) 6–17
9. Hui, Q., Haddad, W.M., Chellaboina, V., Hayakawa, T.: Adaptive control of mammilary drug delivery systems with actuator amplitude constraints and system time delay. European Journal of Control **11**(6) (2005) 1–15
10. Mendonça, T., Lemos, J.M., Magalhães, H., Rocha, P., Esteves, S.: Drug delivery for neuromuscular blockade with supervised multimodel adaptive control. IEEE Transactions on Control Systems Technology **17**(6) (Nov. 2009) 1237–1244
11. Balas, G., Chiang, R. Packard, A., Safanov, M.: Robust Control Toolbox^{TM}User's Guide. The MathWorks, Inc. (2012)