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New approach for the control of anesthesia based on dynamics decoupling

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Abstract: This paper deals with a new strategy for the control of anesthesia taking into account the saturation of the actuator and the target interval tolerated for the depth of anesthesia during a surgery. In addition, to take into account multiple time scale dynamics in the anesthesia model, the system is re-expressed by decoupling the fast dynamics from the slow ones. These slow dynamics are then considered as disturbances for the fast system. Similarly the fast states correspond to disturbances for the slow subsystem. Taking into account the variability of the patient by using the polytopic uncertainty framework, robust control design is proposed through quasi-LMI (linear matrix inequalities) conditions. The characterization of domains of stability and invariance for both the slow and fast subsystems is provided. Then associated convex optimization issues are discussed. Finally, the theoretical conditions are evaluated on a panel of simulated patients.

Keywords: Anesthesia, saturated control, multiple time scale dynamics, robustness.

1. INTRODUCTION

General anesthesia consists in the control of the anesthetic and analgesic states of the patient by adjusting the perfusion of hypnotics and/or analgesics based on clinical indicators such as heart rate, blood pressure and BIS (Bispectral index, derived from the spectral analysis of the electroencephalogram signal (EEG)). The idea of controlling the injection of anesthetic drugs for maintaining an adequate anesthetic state during surgery was already proposed in Soltero et al. (1951). In the clinical practice, however, few things have changed, and the control of the depth of anesthesia continues to be done mainly by the anesthesiologist. The difficulty to adopt a new system is that it should demonstrate a safety guarantee and clinical benefits for patients and provide significant advantages compared to existing methods including manual ones (see, for example, Manberg et al. (2008)).

Thus, the problem of closed-loop control of the depth of anesthesia of a patient is a very challenging problem due to the numerous phenomena to be considered as patient variability, multivariable characteristics, positivity constraints, dynamics dependent on the hypnotic agent, ... as pointed out in Bailey and Haddad (2005) and Nascu et al. (2015). Several works have been done in this area through various types of control algorithms: see, for example, Lemos et al. (2014), van Heusden et al. (2014a) for an overview. Let us point out some references in this topic. On the one hand, PID-based feedback control strategies

have been followed to adjust the amount of Propofol administered (Absalom et al. (2002), Absalom and Kenny (2003), Soltész (2013)). On the other hand, given the significant variability in the models established for the anesthesia, adaptive control techniques appear quite appropriate. Thus, based on the properties of non-negative linear dynamic systems, Haddad et al. (2003) proposed an adaptive control strategy to ensure the asymptotic stability of a target equilibrium point and also to ensure the positivity of the closed loop system states. Other alternative ways are the design of robust controllers as shown in Lemos et al. (2014) or the use of model predictive control as proposed in van Heusden et al. (2014a).

This paper revisits the control problem of the anesthetic state of a patient under the framework of saturated systems. The fact to take into account the saturation of the input in the context of anesthesia has been emphasized in van Heusden et al. (2014b). The global goal is then to control the BIS in an interval fixed a priori, taking into account directly the magnitude limitation of the control signal, that is the limitation of the rate of drug addition (in the current case the Propofol) intravenously. The saturated control systems is therefore the theoretical framework of this work (see Tarbouriech et al. (2011) and references therein). Moreover, the dynamics of the evolution of the drug in the patient is usually described by a pharmacokinetic model with multiple time scales. Rather than treating the system as a singularly

perturbed system (Kokotovic et al. (1986)), we reformulate the problem by separating fast and slow dynamics in order to reduce the global control problem to that of the fast subsystem (BIS being directly linked to the states of the fast subsystem) perturbed by the slow dynamics. Actually, the slow dynamics are then considered as disturbances for the fast system, whereas in the same time the fast states correspond to disturbances for the slow subsystem. This is justified by the fact that the depth of anesthesia is a direct function of the states of the fast dynamics. Taking into account the variability of the patient thanks to the polytopic uncertainty framework, the main contribution of the paper resides in the robust control design proposed through quasi-LMI (linear matrix inequalities) conditions. The design of a state feedback control law together with the characterization of domains of stability and invariance for both the slow and fast subsystems is thus provided from these conditions.

2. MODELLING ASPECTS AND PROBLEM FORMULATION

2.1 The traditional patient model

The compartment model used to describe the circulation of drugs in a patient's body is based on a three-compartment model as shown in Figure 1 from Glass et al. (1989). The first compartment is the central compartment in which the drug is administered. It is formed mainly by the intravenous blood. The other two compartments constitute muscle and fat. This model assumes that the system is represented by various compartments, the drug being transported from one compartment to another one and its elimination being done by the metabolic process.

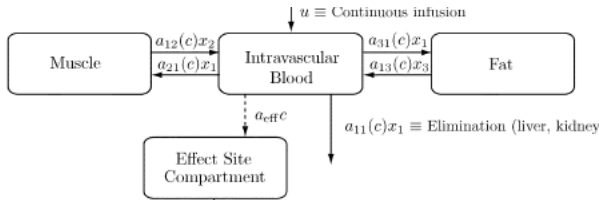


Fig. 1. The three compartments model

The effect of the drug on the patient is expressed through-out the effect site, which represents the action of drugs on the brain. This action is expressed through the concentration at the effect site (denoted C_{eff}) directly related to the concentration in the central compartment (Figure 1) through a first order dynamics:

$$\begin{aligned} \dot{C}_{eff}(t) &= K_{e0}(x_1(t)/V_c - C_{eff}(t)), \\ C_{eff}(0) &= x_1(0)/V_c \geq 0, \end{aligned}$$

Then, the compartmental model can be expressed as follows:

$$\dot{x}_{an}(t) = Ax_{an}(t) + Bu_{an}(t), \quad x_{an}(0) \geq 0 \quad (1)$$

with

$$A = \begin{bmatrix} -K_{e0} & K_{e0}/V_c & 0 & 0 \\ 0 & -(a_{11} + a_{21} + a_{31}) & a_{12} & a_{13} \\ 0 & a_{21} & -a_{12} & 0 \\ 0 & a_{31} & 0 & -a_{13} \end{bmatrix}$$

$$B = [0 \ 1 \ 0 \ 0]'$$

where $x_{an} = [C_{eff} \ x_1 \ x_2 \ x_3]'$, $x_1(t)$, $x_2(t)$, $x_3(t)$ are the masses in grams of the propofol in the different compartments and u_{an} is the infusion rate in g/min of the anesthetic.

The parameters $a_{ij} \geq 0$, $\forall i \neq j$, $i, j = 1, 2, 3$, are the transfer rates of the drug between compartments. The parameter a_{11} represents the rate of elimination from the central compartment. These parameters are functions of the patient characteristics (weight, age, height, ...). There exists several empirical models, which give the relation between those parameters and patient's characteristics (Coppens et al. (2011)). In particular one can cite the model of Schneider et al. (1998) that we use here to define a typical patient and to build uncertain models to represent the inter-patient variability.

The depth of anesthesia indicator widely used by clinicians is the *BIS* (the bispectral index). It is a signal derived from the EEG analysis, which quantifies the level of consciousness of a patient from 0 (no cerebral activity) to 100 (fully awake patient). The relationship between the concentration at the effect site (C_{eff}) and the *BIS* can be described empirically by a decreasing sigmoid function (Bailey and Haddad (2005)):

$$BIS(C_{eff}(t)) = BIS_0 \left(1 - \frac{C_{eff}^\gamma(t)}{C_{eff}^\gamma(t) + EC_{50}^\gamma} \right), \quad (2)$$

The BIS_0 is the *BIS* value of an awake patient typically set to 100, EC_{50} corresponds to drug concentration associated with 50% of the maximum effect and γ is a parameter modeling the degree of non-linearity. Typical values for these parameters are $EC_{50} = 3.4 \mu\text{g/ml}$ and $\gamma = 3$. This relationship is illustrated in Figure 2.

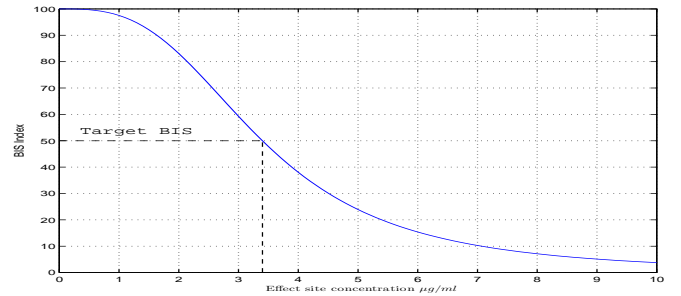


Fig. 2. BIS Index versus effect site concentration.

Note, however, that the chosen three-compartment model is one example of compartment models. It has been chosen for its simplicity and its good representativity even if there exist other models of different complexity for the propofol - *BIS* relation Lemos et al. (2014). Furthermore, to be more realistic, the model considered should include a time-delay. Such aspect will be studied in the future.

2.2 Model uncertainties

In the traditional model introduced above, also known as Pharmacokinetic/Pharmacodynamic (PK/PD) model, it is customary to distinguish between two different types of uncertainty: the uncertainty caused by inter-patient variability (i.e., the variability observed between different

individuals), and the uncertainty originating from intra-patient variability (i.e., the variability observed within one particular individual).

In this work, we focus only on the inter-patient variability with the use of Schnider model (Table 1) to predict the PK/PD model parameters. The lean body mass (LBM) is calculated using the James formula [James (1976)] as follows:

$$\begin{aligned} \text{Male: LBM} &= 1.1 \times \text{weight} - 128 \times (\text{weight}/\text{height})^2 \\ \text{Female: LBM} &= 1.07 \times \text{weight} - 148 \times (\text{weight}/\text{height})^2 \end{aligned}$$

Only three of the model parameters are dependent of the patient's characteristics (a_{11}, a_{12}, a_{21}) . Thus, for a given range of patients, the uncertainties of the A matrix can be included in a polytope with $N = 2^3 = 8$ vertices, that is:

$$A = \sum_{i=1}^N \lambda_i A^{[i]}, \quad \text{with} \quad \sum_{i=1}^N \lambda_i = 1, \quad \lambda_i \geq 0 \quad (3)$$

with $A^{[i]}$ corresponding to the vertices of the polytope in which A is defined.

2.3 Equilibrium point

We consider generally that during a surgery, the *BIS* must be brought then maintained close to 50, or at least in an interval between 40 and 60. Given the sigmoid describing the relation between the *BIS* and the effect site concentration, it follows that for the *BIS* equal to 50% of BIS_0 the effect site concentration must be equal to EC_{50} . The values of the other variables can then be deduced from the equilibrium point of system (1). Indeed, if we set $A = [A_1 \ A_2 \ A_3 \ A_4]$ where A_i is the i^{th} column of A and setting $C_{effe} = EC_{50}$, it follows from (1) that, at equilibrium:

$$[A_2 \ A_3 \ A_4 \ B] [x_{e1} \ x_{e2} \ x_{e3} \ u_e]' + A_1 EC_{50} = 0. \quad (4)$$

Noting that the matrix $[A_2 \ A_3 \ A_4 \ B]$ is non-singular, there exists a unique solution satisfying the equation (4). We can thus deduce the value of the state variables at equilibrium

$$x_{e1} = C_{effe} V_c, \quad x_{e2} = \frac{a_{21}}{a_{12}} x_{e1}, \quad x_{e3} = \frac{a_{31}}{a_{13}} x_{e2}$$

and the value of the input for this equilibrium is given by

$$u_e = a_{11} x_{e1}$$

The equilibrium point actually depends on the patient parameters. Then in the sequel we consider a mean equilibrium point corresponding to a nominal patient belonging to the patient set.

2.4 Error model

From the system (1) and the target equilibrium point $x_e = [C_{effe} \ x_{e1} \ x_{e2} \ x_{e3}]'$ that we seek to stabilize, by a change of variable, $x_{err} = x_{an} - x_e$ and $u_{err} = u_{an} - u_e$, the error model can be described as:

$$\dot{x}_{err} = Ax_{err} + Bu_{err} \quad (5)$$

with $x_{err} = [c_{eff} \ x_{err1} \ x_{err2} \ x_{err3}]'$ and A defined in equation (3).

The positivity constraints on u_{an} and x_{an} can be viewed as interval constraints on u_{err} and x_{err} . Indeed, from the definition of x_{err} and u_{err} :

$$x_{an} \geq 0 \Rightarrow x_{err} \geq -x_e$$

$$u_{an} \geq 0 \Rightarrow u_{err} \geq -u_e$$

Moreover, it will also be taken into account an upper limit on the amount of drugs that can be injected in the blood over time.

2.5 Problem formulation

In general, the monitoring done by the anesthetist to bring the patient to the desired anesthetic state ($BIS = 50$) is decomposed in two phases. The first one, called induction, consists in administering bolus doses of drugs to quickly bring the patient to unconsciousness and not too far from the set point (Lemos et al. (2014)). The second one is the maintenance phase. A constant injection rate (open loop) close to the equilibrium input (knowing that it is patient-dependent and therefore unknown) is selected. It is up to the anesthetist, who does the controller job, to adjust the input rate according to the output signal. In this work, we focus on the second phase, i.e we propose a closed-loop control strategy after the first injection by the anesthetist, to keep then the patient in the desired target interval. Furthermore, we aim at ensuring the robustness of this strategy for some range of adult patients. The problem we intend to solve can then be formulated as follows:

Problem 1. Find a saturated robust state feedback control $u_{err} = \text{sat}(Kx_{err})$, for the uncertain system (5), in order to bring the system output (the *BIS*) to its set-point and maintain the trajectories confined in an invariant domain including this target.

2.6 Multiplicity of dynamics

Furthermore, regardless of patient under consideration, the dynamics of metabolism and circulation of propofol in the central compartment and at the site effect is ten times faster than in muscles, and even a hundred times faster than in fat. Feedback designs for such systems suffer from high dimensionality and ill-conditioning (Khalil (1987)).

One way to address this problem would be to consider the system as a singularly perturbed system (Kokotovic et al. (1986)). Many studies have addressed the synthesis of controllers for singularly perturbed systems, and most often considering the control of the slow dynamics as the crucial problem. In our case, the control of the fast dynamics is the most important because the regulation of the *BIS* is a direct function of the concentration at the effect site and thus of the fast dynamics on which the administered drug directly acts. Thus, in the following, we choose an alternative route to separate slow and fast dynamics. The approach pursued is to synthesize a controller for the fast dynamics, considering the slow dynamics as a bounded perturbation of the system.

3. CONTROLLER SYNTHESIS

As mentioned before, the particular structure of the system allows us to split it into two subsystems, namely a fast subsystem (central compartment (blood), effect site), on which acts the control input, and a slow subsystem (muscles and fat compartments) whose dynamics is influenced only by the state of the fast subsystem (Figure 3). The slow subsystem is then considered as a simple disturbance for the fast subsystem.

Table 1. Schnider Model

Parameter	Estimation	male, 53yr, 77kg, 177cm
$a_{11}(\text{min}^{-1})$	$0.443 + 0.0107 \times (\text{weight}-77) - 0.0159 \times (\text{LBM}-59) + 0.0062 \times (\text{height}-177)$	0.384
$a_{12}(\text{min}^{-1})$	$0.302 - 0.0056 \times (\text{age}-53)$	0.375
$a_{13}(\text{min}^{-1})$	0.196	0.196
$a_{21}(\text{min}^{-1})$	$[1.29 - 0.024 \times (\text{age}-53)] / [18.9 - 0.391 \times (\text{age}-53)]$	0.067
$a_{13}(\text{min}^{-1})$	0.0035	0.0035
$K_{e0}(\text{min}^{-1})$	0.456	0.456

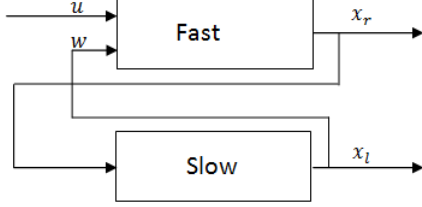


Fig. 3. The whole system with the fast subsystem perturbed by the slow dynamics

Thus, if we denote $x_f = [c_{eff} \ x_{err1}]'$ the fast states and $x_s = [x_{err2} \ x_{err3}]'$ the slow states, the system (5) can be written as follow:

$$\dot{x}_f = A_f x_f + A_{fs} x_s + B_f u \quad (6a)$$

$$\dot{x}_s = A_{sf} x_f + A_s x_s \quad (6b)$$

with uncertain matrices A_f , A_s , A_{fs} and A_{sf} defined using the formalism of equation (3).

We seek to synthesize a state feedback controller for the fast subsystem of the form:

$$u = \text{sat}(Kx_f) = \text{sign}(Kx_f) \min\{u_0, |Kx_f|\} \quad (7)$$

considering that the slow states act as simple disturbances. The synthesis of the state feedback controller and the determination of the associated asymptotic stability domain are done by the following proposition, denoting n_f , n_s and m the dimensions of the fast subsystem, the slow subsystem and the controller.

Proposition 1. If there exist two symmetric positive definite matrices $W \in \mathfrak{R}^{n_f \times n_f}$, $R \in \mathfrak{R}^{n_s \times n_s}$, a positive diagonal matrix $S \in \mathfrak{R}^{m \times m}$, two matrices $Y \in \mathfrak{R}^{m \times n_f}$, $Z \in \mathfrak{R}^{m \times n_f}$ and six positive scalars $\tau_1, \tau_2, \tau_3, \tau_4, \eta$ and δ satisfying¹:

$$\begin{bmatrix} WA_f^{[i]'} + A_f^{[i]}W + B_f Y + Y' B_f' + \tau_1 W & \star & \star \\ SB_f' - Z & -2S & \star \\ RA_{fs}^{[i]'} & 0 & -\tau_2 R \end{bmatrix} < 0 \quad (8)$$

$i = 1, \dots, N$

$$\begin{bmatrix} RA_s^{[i]'} + A_s^{[i]}R + \tau_3 R & A_{sf}^{[i]'}W \\ WA_{sf}^{[i]'} & -\tau_4 W \end{bmatrix} < 0 \quad i = 1, \dots, N \quad (9)$$

$$\begin{bmatrix} W & Y_{(j)} - Z_{(j)}' \\ Y_{(j)} - Z_{(j)} & \eta u_{0(j)}^2 \end{bmatrix} \geq 0, \quad j = 1, \dots, m \quad (10)$$

$$-\tau_1 \delta + \tau_2 \eta < 0 \quad (11)$$

¹ In symmetric matrices of the proposition, the notation \star corresponds to symmetric blocks.

$$-\tau_3 \eta + \tau_4 \delta < 0 \quad (12)$$

then, the gain $K = YW^{-1}$ is such that for any $x_s \in \mathcal{E}(R^{-1}, \delta) = \{x_s \in \mathbb{R}^{n_s}; x_s' R^{-1} x_s \leq \delta^{-1}\}$, the trajectories of the uncertain saturated system (6a)-(7) do not leave the ellipsoid $\mathcal{E}(W^{-1}, \eta) = \{x_f \in \mathbb{R}^{n_f}; x_f' W^{-1} x_f \leq \eta^{-1}\}$. Also, the trajectories of the slow subsystem (6b) remain in the ellipsoid $\mathcal{E}(R^{-1}, \delta)$ for any $x_f \in \mathcal{E}(W^{-1}, \eta)$.

Proof: The proposition extends the results published in Tarbouriech et al. (2011) to the case of the system (6) with decoupled fast and slow dynamics. Thus, one has to prove, at the same time, that the trajectories of the fast subsystem under control remain confined in $\mathcal{E}(W^{-1}, \eta)$ for all trajectories of the slow subsystem themselves confined in $\mathcal{E}(R^{-1}, \delta)$.

Consider for the fast subsystem the quadratic Lyapunov function $V(x_f) = x_f' W^{-1} x_f$, $W = W' > 0$. One has to prove that $\dot{V}(x_f) < 0$ for any x_f such that $x_f \notin \text{int}(\mathcal{E}(W^{-1}, \eta))$, and any $x_s \in \mathcal{E}(R^{-1}, \delta)$. In other words, we have to verify by using the S-procedure the following inequality:

$$\dot{V}(x_f) + \tau_1 (x_f' W^{-1} x_f - \eta^{-1}) + \tau_2 (\delta^{-1} - x_s' R^{-1} x_s) < 0 \quad (13)$$

Moreover, we use the modified sector condition (Tarbouriech et al. (2011)), which expresses that for any x_f belonging to the polyhedron $S(|K - G|, u_0)$ defined by:

$$S(|K - G|, u_0) = \{x_f \in \mathfrak{R}^{n_f}; -u_0 \leq (K - G)x_f \leq u_0\}$$

the sector condition

$$\phi(Kx_f)' S^{-1} (\phi(Kx_f) + Gx_f) \leq 0$$

is verified, with $\phi(Kx_f) = \text{sat}(Kx_f) - Kx_f$, and S a positive diagonal matrix.

Thus, a sufficient condition to verify (13) is that

$$\dot{V}(x_f) + \tau_1 x_f' W^{-1} x_f - \tau_2 x_s' R^{-1} x_s - 2\phi(Kx_f)' S^{-1} (\phi(Kx_f) + Gx_f) < 0 \quad (14)$$

and

$$-\tau_1 \eta^{-1} + \tau_2 \delta^{-1} < 0 \quad (15)$$

as long as $\mathcal{E}(W^{-1}, \eta) \subseteq S(|K - G|, u_0)$, which is ensured by satisfying the inequality (10). By denoting $Z = GW$ and $Y = KW$, the inequality (14) can be written as (16) (given at the top of next page). Thanks to the polytopic representation of the uncertain matrix A (and subsystems A_f, A_{fs}, A_s, A_{sf}), (16) is satisfied if the inequality (8) holds at each vertex i . The satisfaction of (8), (10) and (11) guarantees the invariance of the ellipsoid $\mathcal{E}(W^{-1}, \eta)$ for the uncertain fast system, for any $x_s \in \mathcal{E}(R^{-1}, \delta)$.

Similarly, the satisfaction of relations (9) et (12) ensures the invariance of the ellipsoid $\mathcal{E}(R^{-1}, \delta)$ for the uncertain slow system, for any $x_f \in \mathcal{E}(W^{-1}, \eta)$.

$$\begin{bmatrix} W^{-1}x_f \\ S^{-1}\phi(Kx_f) \\ x_s \end{bmatrix}' \begin{bmatrix} W(A_f + B_fK)' + (A_f + B_fK)W + \tau_1 W B_f S - Z' & A_{fs} \\ SB_f' - Z & -2S & 0 \\ A_{fs}' & 0 & -\tau_2 R \end{bmatrix} \begin{bmatrix} W^{-1}x_f \\ S^{-1}\phi(Kx_f) \\ x_s \end{bmatrix} < 0 \quad (16)$$

Furthermore, the satisfaction of the relation (8) implies that the matrix $A_f + B_fK$ is Hurwitz. ■

4. NUMERICAL EXAMPLE

For a wide range of adult patients, male and female, whose age varies between 20 and 70, weight between 50 and 100 kg and height between 140 and 200 cm, the uncertain parameter intervals, calculated with the Schnider model, are given in Table 2 and used to define the eight vertices of the polytope.

Param	a_{11}	a_{12}	a_{21}
interval	[0.2497, 0.8982]	[0.2066, 0.4876]	[0.0655, 0.0720]

Table 2. Uncertain parameters intervals

Proposition 1 then allows us to synthesize a saturated state feedback controller and characterize invariant sets for both the slow and the fast uncertain subsystems. Moreover, We are seeking to maintain the BIS in the range [40, 60] which corresponds to impose limits on the effect site concentration:

$$c_{e_{min}} \leq c_{eff} \leq c_{e_{max}} \quad (17)$$

with $c_{e_{min}} = -c_{e_{max}} = 0.5$.

These constraints can be written as follows:

$$\mathcal{P} = \{x_r \in \mathbb{R}^2 : |a_k^T x_r| \leq 1, \quad k = 1, \dots, q_r\}$$

and the LMI condition,

$$a_k' W a_k \leq \eta, \quad k = 1, \dots, q. \quad (18)$$

ensures that $\mathcal{E}(W^{-1}, \eta) \subset \mathcal{P}$ (Boyd et al. (1994)). The purpose of the synthesis is to maximize the invariant domain for the fast subsystem up to the BIS limit associated to (17) and the admissible set of the fast system disturbances (i.e. the invariant set of the slow system), eventually to include the initial state $x_{es} = [-x_{e2} \quad -x_{e3}]'$ of the slow system. In practice, it is not necessary to include this initial slow state as soon as thanks to a first injection in the blood, the drug accumulates in the other compartments and we are just aiming at including a percentage of the initial condition through the constraint below:

$$\begin{bmatrix} \delta & \kappa \delta x_{el}' \\ \kappa \delta x_{el} & R \end{bmatrix} \geq 0 \quad (19)$$

with $\kappa \in [0, 1]$.

Finally, an LMI condition is added in order to limit $\|K\|_2$ by $\sqrt{\sigma}$ (see Appendix):

$$\begin{bmatrix} \sigma I & Y \\ Y' & 2W - I \end{bmatrix} \geq 0 \quad (20)$$

A solution to Problem 1 is given by the following optimization problem:

$$\begin{aligned} \min & -Trace(W) + \eta \\ \text{sous} & (8) - (12), (18) - (20) \end{aligned}$$

By setting $\tau_1 = 0.5, \tau_2 = 0.5, \tau_3 = 0.0021, \tau_4 = 0.002$, the fast system invariant set associated to the uncertain system with parameters bounds given in Table 2 is plotted in dashed lines in Figure 4. It may be compared to the solution obtained with an average male patient (53 years, 77 kg, 177 cm), plotted in solid line in Figure 4.

To evaluate the source of the gap between the two sets, we also solve the problem by considering a small interval for one patient characteristics (height, weight or age) and the full uncertainty for the other ones. The results exhibit that the range of weight and size, or the sex of the patient have not much influence on the size of the fast system invariant sets (see Figure 4 for the case where a small interval of 75-80 kg is considered (dash-dotted line)). On the other hand, the age seems to have a strong influence on the size of the ellipsoid (see Figure 4, range of 50-55 year in dotted line).

Similar results are obtained for invariant sets of the slow system (not shown here).

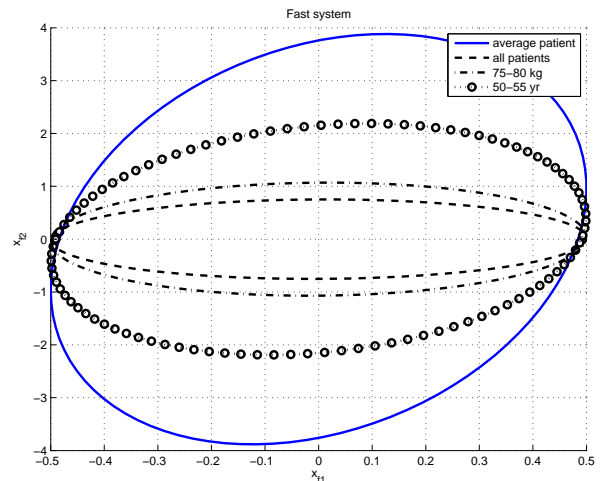


Fig. 4. The invariant set of the fast system $\mathcal{E}(W^{-1}, \eta)$.

To be fair, it is important to point out that the size of the invariant sets for a single patient is mainly correlated with the age of patient. Indeed, the younger is the patient the smaller are the sets.

To illustrate the whole strategy of control, Figure 5 gives the BIS response for bolus injection of 1.5 mg/kg administered during the 30 first seconds, followed by the state feedback control synthesized above. It may be checked that this controller ensures that all patients BIS response converge to 50 and stay in the target interval [40, 60].

5. CONCLUSION

In this paper, we presented a state feedback controller synthesis approach for a decoupled model for anesthesia. The decomposition of the model into a fast and a slow systems allows to focus the control design on the fast subsystem,

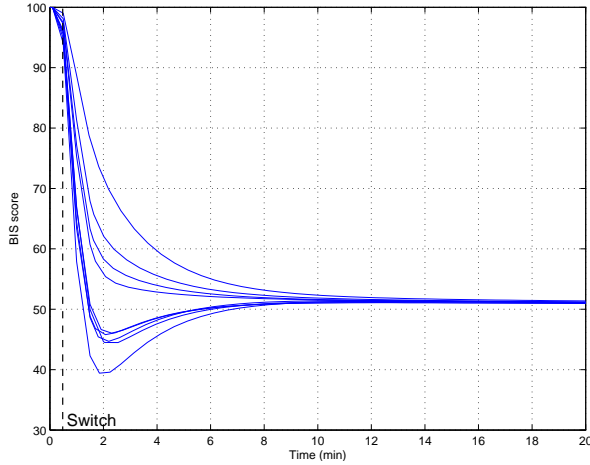


Fig. 5. The BIS score for different adult patients.

whereas the slow one is considered as a disturbance. The results express the strong influence of the age of the patient on the size of the invariance sets, and suggest to consider smaller sets of patient characteristics to adapt the control gain to each set of patients.

The next step will be to extend the approach to the output dynamic feedback design, in order to better cope with the real-life case. Moreover, the synthesized controller guarantees to keep the BIS in the range $[40,60]$ but does not address the induction phase corresponding to the first drug injection produced by the anesthetist. To finalize the automation of the entire process, the next step will be to propose a switched control law inspired by the practice. From a theoretical point of view we seek to ensure a priori the stability and performance of such a control system.

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APPENDIX

To bound the norm $\|K\|_2$ by $\sqrt{\sigma}$, on can write:

$$K'K = W^{-1}Y'YW^{-1} \leq \sigma I \quad (21)$$

$$\Leftrightarrow \sigma I - W^{-1}Y'YW^{-1} \geq 0 \quad (22)$$

By using Schur complement, (22) can be expressed :

$$\begin{bmatrix} \sigma I & Y \\ Y' & W^2 \end{bmatrix} \geq 0 \quad (23)$$

Otherwise, by using the perfect square condition:

$$(W - I)(W - I) \geq 0 \quad (24)$$

$$\Leftrightarrow W^2 \geq 2W - I \quad (25)$$

We then obtain that (20) is a sufficient condition for (23) and therefore satisfy the condition on the norm 2 of K .