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Reference tracking controller design for anesthesia

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Abstract: This paper addresses the problem of tracking a constant BIS reference during anesthesia taking into account control input saturation, multiple time scale dynamics and inter-patient variability. LMIs conditions are proposed to compute a state feedback involving an integral action to ensure a perfect output tracking. These conditions guarantee that the trajectories of the closed-loop system remain in an invariant ellipsoidal set. The theoretical conditions are numerically illustrated on a set of adult patients as a proof of principle.

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

1. INTRODUCTION

General anesthesia generally involves three functional components: hypnosis (unconsciousness), analgesia (absence of sensation) and areflexia (lack of movement, immobility). A well balanced anesthesia consists in the control of those three components by adjusting the perfusion of drugs based on clinical indicators such as heart rate, blood pressure, pupil response and BIS (Bispectral index, derived from the spectral analysis of the electroencephalogram signal (EEG)).

Roughly speaking, the control of anesthesia has to take into account numerous phenomena such 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). Literature on control of anesthesia has often been devoted to one component, hypnosis, with the objective to adjust the amount of propofol administered (Lemos et al. (2014), Van Heusden et al. (2014), Absalom and Kenny (2003), Haddad et al. (2003), Zhusubaliyev et al. (2014), Zabi et al. (2015)). Note also that, thanks to a certain maturity in PID or adaptive controller designs, clinical tests have illustrated the interest of closed-loop anesthesia control (Van Heusden et al. (2014), Le Guen et al. (2014), Biswas et al. (2013), Rocha et al. (2014)).

This paper fits as a logical continuation of these works. The backbone of the contribution resides in the reformulation of the control problem of anesthesia in the robust and saturated control framework (Tarbouriech et al. (2011)). More specifically, the overall objective is to control the BIS and track references in an interval fixed a priori, taking into account directly the limitation of the rate of drug addition (in the current case the Propofol) intravenously. Moreover, the dynamics of the drug in the patient's body is usually described by a pharmacokinetic model with multiple time scales. The problem is solved by separating fast and slow dynamics in order to reduce the global control problem to that one of the fast subsystem (BIS being directly

linked to the states of the fast subsystem) perturbed by the slow 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 for a BIS reference tracking proposed through quasi-LMI (linear matrix inequalities) conditions. Furthermore, to ensure the reference tracking for the BIS (zero static error), an integral action is added. The design of a dynamic output-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.

Notation. The notation throughout the paper is standard. For a vector x or a matrix A , x' and A' denote the transpose of x and A , respectively. For two symmetric matrices of the same dimensions, A and B , $A > B$ means that $A - B$ is symmetric positive definite. For a matrix A , $He(A) = A' + A$ and $\text{trace}(A)$ denotes its trace. I and 0 stand respectively for the identity and the null matrix of appropriate dimensions. For a partitioned matrix, the symbol \star stands for symmetric blocks. $|\cdot|$ stands for the absolute value.

2. MODELING ASPECTS

2.1 The patient model

The model used to describe the circulation of drugs in a patient body is based on a three-compartment model, known as Pharmacokinetic/Pharmacodynamic (PK/PD) model, to which is added the dynamics of drugs at the effect site representing of the action of drugs on the brain (Beck (2015)). Let us consider the state $x_{bis}(t)$ composed with the effect site concentration x_{bis1} and the masses in grams of the anesthetic drug in the different compartments (x_{bis2} , x_{bis3} , x_{bis4}). The dynamics of anesthesia can then be expressed as follows:

$$\dot{x}_{bis}(t) = \mathbb{A}x_{bis}(t) + \mathbb{B}u_{bis}(t) \quad (1)$$

with

$$\mathbb{A} = \begin{bmatrix} -k_{e0} & k_{e0}/V_1 & 0 & 0 \\ 0 & -(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} \\ 0 & k_{12} & -k_{21} & 0 \\ 0 & k_{13} & 0 & -k_{31} \end{bmatrix}$$

$$\mathbb{B} = [0 \ 1 \ 0 \ 0]'$$

where $u_{bis}(t)$ is the infusion rate of propofol (mg/min).

The depth of anesthesia indicator widely used by clinicians is the BIS (the bispectral index), a signal derived from the EEG analysis which quantifies the level of consciousness of a patient from 0 (no cerebral activity) to y_{bis0} (fully awake patient), this value being typically set to 100. The relationship between the concentration at the effect site (x_{bis1}) and the BIS can be described empirically by a decreasing sigmoid function (Bailey and Haddad (2005)):

$$y_{bis}(x_{bis1}(t)) = y_{bis0} \left(1 - \frac{x_{bis1}^\gamma(t)}{x_{bis1}^\gamma(t) + EC_{50}^\gamma} \right) \quad (2)$$

In (2), EC_{50} corresponds to the drug concentration associated with 50% of the maximum effect and γ is a parameter modeling the degree of nonlinearity. Typical values for these parameters are $EC_{50} = 3.4\mu g/ml$ and $\gamma = 3$.

2.2 Model uncertainties

In the model above described, 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). This work focuses on the inter-patient variability and, among various existing models which express the model parameters as functions of the patient characteristics (weight, age, height, ...), Schnider's model (Schnider et al. (1998)) is used to define the patient dynamics in presence of hypnotic drugs (see Table 1). The lean body mass (LBM) is calculated using the James formula (James (1976)) as follows:

$$\text{Male: LBM} = 1.1 \times \text{weight} - 128 \times (\text{weight}/\text{height})^2$$

$$\text{Female: LBM} = 1.07 \times \text{weight} - 148 \times (\text{weight}/\text{height})^2$$

Three of the model parameters used in matrix \mathbb{A} are dependent of the patient characteristics (k_{10}, k_{12}, k_{21}). Thus, for a given range of patients, the uncertainties of matrix \mathbb{A} (and further of sub-matrices issued from \mathbb{A}) can be included in a polytope with $N = 2^3 = 8$ vertices, that is:

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

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

2.3 Central (nominal) equilibrium

During a surgery, the BIS is generally brought then maintained close to 50, or eventually in an interval between 40 and 60 according to the pain of the intervention. Thus, as shown in Zabi et al. (2015), it follows that for $y_{eq} = y_{bis}(EC_{50})$, the effect site concentration is equal to EC_{50}

and there exists a unique associated equilibrium defined as follows:

$$\begin{aligned} x_{eq} &= \left[EC_{50} \quad V_1 EC_{50} \quad \frac{k_{12}}{k_{21}} V_1 EC_{50} \quad \frac{k_{13}}{k_{31}} V_1 EC_{50} \right]' \\ u_{eq} &= k_{10} V_1 EC_{50} \end{aligned} \quad (4)$$

Moreover, in the sequel, we consider the linearized BIS function around this equilibrium given by Haddad et al. (2003):

$$\begin{aligned} y_{bis}(x_{bis1}(t)) &= y_{eq} + \mathbb{C}(x_{bis}(t) - x_{eq}) \\ &= y_0 + \mathbb{C}x_{bis}(t) \end{aligned} \quad (5)$$

with $y_0 = 125$, $\frac{1}{k_{bis}} = -22.06$ and $\mathbb{C} = [\frac{1}{k_{bis}} \ 0 \ 0 \ 0]$.

Being concerned with the uncertainty on the patient characteristics (k_{10}, k_{12}, k_{21}), one has actually to deal with a set of equilibrium points around the nominal equilibrium point described in (4), corresponding to each value of the parameters.

2.4 Both fast and slow dynamics

For any patient, the dynamics of the metabolism and of the drug circulation 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. Many studies have addressed the synthesis of controllers for systems with such slow and fast dynamics, named singularly perturbed systems (Kokotovic et al. (1987)), often considering that the control of the slow dynamics is the key problem. In anesthesia, the control of the fast dynamics is the most important one because 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, an alternative route to separate slow and fast dynamics is followed: a controller is designed for the fast dynamics, considering the slow dynamics as a bounded perturbation of the system.

3. PRELIMINARIES

3.1 Control structure

As previously mentioned, the control objective corresponds to bring the BIS to a given reference, namely 50, then eventually to track step references y_{ref} in the interval 40 - 60. A change of coordinate is then considered to work around the central equilibrium x_{eq} and the error state vector is decomposed into a fast state $x_f = [x_{bis1} - x_{eq1} \ x_{bis2} - x_{eq2}]'$ and a slow state $x_s = [x_{bis3} - x_{eq3} \ x_{bis4} - x_{eq4}]'$ around the nominal equilibrium.

The input and output of the error system are $u = u_{bis} - u_{eq}$ and $y_f = y_{bis} - y_{eq}$, respectively, and the tracking reference becomes $r = y_{ref} - y_{eq}$. Moreover, it must be taken into account that u_{eq} is patient-dependent and therefore its value is related to the uncertainty of the dynamics (as pointed out in Section 2.3) and reference-dependent. Then, one considers in the following that $u = u_f + w_f$, where $u_f = u_{bis} - u_0$ denotes the control input and $w_f = u_0 - u_{eq}$ denotes a disturbance. Actually, u_0 is defined as the "worst" patient and reference case input, such as $u_0 \leq u_{eq}$, for any patient and reference in an *a priori* given interval.

Table 1. Schnider Model

Parameter	Estimation	male, 53yr, 77kg, 177cm
$k_{10}(\text{min}^{-1})$	$0.443 + 0.0107 \times (\text{weight}-77) - 0.0159 \times (\text{LBM}-59) + 0.0062 \times (\text{height}-177)$	0.384
$k_{12}(\text{min}^{-1})$	$0.302 - 0.0056 \times (\text{age}-53)$	0.375
$k_{13}(\text{min}^{-1})$	0.196	0.196
$k_{21}(\text{min}^{-1})$	$[1.29 - 0.024 \times (\text{age}-53)] / [18.9 - 0.391 \times (\text{age}-53)]$	0.067
$k_{31}(\text{min}^{-1})$	0.0035	0.0035
$k_{e0}(\text{min}^{-1})$	0.456	0.456

With such a notation, considering any input $u_f \geq -u_0$ guarantees, by construction, that $u_{bis} \geq 0$.

Then, the error system issued from (1)-(5) can be rewritten as follows:

$$\begin{aligned} \dot{x}_f(t) &= A_f x_f(t) + A_{fs} x_s(t) + B_f u_f(t) + B_f w_f(t) \\ \dot{x}_s(t) &= A_{sf} x_f(t) + A_s x_s(t) \\ y_f(t) &= C_f x_f(t) \\ e(t) &= k_{bis}(y_f(t) - r) = [1 \ 0] x_f(t) - k_{bis} r \end{aligned} \quad (6)$$

with $x_f \in \mathbb{R}^{n_f}$, $u_f \in \mathbb{R}$, $y_f \in \mathbb{R}$, $x_s \in \mathbb{R}^{n_s}$, $r \in \mathbb{R}$ and $e \in \mathbb{R}$ ($n_f = n_s = 2$). Furthermore, matrices A_f , A_s , A_{fs} , A_{sf} , B_f and C_f are directly issued from the decomposition of matrices \mathbb{A} , \mathbb{B} and \mathbb{C} defined in Section 2.

Let us augment the system with an integral term ξ in order to guarantee that the output tracks a constant reference in steady state without bias. It is defined by

$$\dot{\xi} = e \quad (7)$$

One can then consider a state-feedback controller

$$y_c = K_c u_c \quad (8)$$

where $u_c \in \mathbb{R}^{n_f+1}$ and $y_c \in \mathbb{R}$ are respectively the input and the output of the controller. The control gain K_c is a constant matrix of appropriate dimensions to be designed. The interconnection between the anesthesia system (6) and the controller (8) is done as follows:

$$\begin{cases} u_f = \text{sat}_{u_0}(y_c) \\ u_c = \begin{bmatrix} e \\ x_{f2} \\ \xi \end{bmatrix}, \end{cases} \quad (9)$$

$\text{sat}_{u_0}(\cdot)$ being the classical saturation function with a symmetric level u_0 defined by $\text{sat}_{u_0}(z) = \text{sign}(z) \min\{u_0, |z|\}$.

As in Flores et al. (2008), we first rewrite system (6) and the integral term with a new state vector $x_{fe}(t) = [e(t) \ x_{f2}(t) \ \xi(t)]' \in \mathbb{R}^n$, $n = n_f + 1$ as follows:

$$\begin{aligned} \dot{x}_{fe}(t) &= A_{fe} x_{fe}(t) + B_{fe} u_f(t) + A_{fse} x_s(t) \\ &\quad + B_{re} r + B_{fe} w_f(t) \\ \dot{x}_s(t) &= A_{sfe} x_{fe}(t) + A_s x_s(t) \end{aligned} \quad (10)$$

with¹

$$\begin{aligned} A_{fe} &= \begin{bmatrix} A_f & 0 \\ [1 \ 0] & 0 \end{bmatrix}, \quad B_{fe} = \begin{bmatrix} B_f \\ 0 \end{bmatrix}, \quad A_{fse} = \begin{bmatrix} A_{fs} \\ 0 \end{bmatrix} \\ B_{re} &= \begin{bmatrix} A_f \begin{bmatrix} k_{bis} \\ 0 \end{bmatrix} \\ 0 \end{bmatrix}, \quad A_{sfe} = [A_{sf} \ 0] \end{aligned}$$

¹ Thanks to the definition of e including the parameter k_{bis} , the matrix M_2 used in Flores et al. (2008) to express the change of variable is equal to the identity matrix and may then be omitted.

Remark 1. The term $A_{sf}[k_{bis} \ 0]'$ which should appear in the right-hand side of the second equation of (10) is omitted as it is equal to zero by construction.

Then, considering the dead-zone nonlinearity

$$\phi(y_c) = \text{sat}_{u_0}(y_c) - y_c,$$

the interconnection of systems (8)-(9)-(10) yields the following dynamics for the closed-loop system

$$\begin{aligned} \dot{x}_{fe} &= (A_{fe} + B_{fe} K_c) x_{fe}(t) + B_{fe} \phi(K_c x_{fe}) \\ &\quad + A_{fse} x_s(t) + B_{re} r + B_{fe} w_f(t) \end{aligned} \quad (11)$$

$$\dot{x}_s = A_{sfe} x_{fe}(t) + A_s x_s(t) \quad (12)$$

or, equivalently, in a more compact form, with $x \in \mathbb{R}^n$, $n = n_f + 1 + n_s$:

$$\dot{x} = (A + BK)x + B\phi(Kx) + B_r r + Bw_f \quad (13)$$

with

$$\begin{aligned} A &= \begin{bmatrix} A_{fe} & A_{fse} \\ A_{sfe} & A_s \end{bmatrix}, \quad B = \begin{bmatrix} B_{fe} \\ 0 \end{bmatrix}, \quad B_r = \begin{bmatrix} B_{re} \\ 0 \end{bmatrix} \\ K &= [K_c \ 0] \end{aligned}$$

3.2 Equilibrium point

In the region of linearity,

$$S(K, u_0) \triangleq \{x \in \mathbb{R}^n; |Kx| \leq u_0\}, \quad (14)$$

system (13) admits the following linear model

$$\dot{x}(t) = (A + BK)x(t) + B_r r + Bw_f \quad (15)$$

Hence, if $(A + BK)$ is Hurwitz, there exists a unique equilibrium in $S(K, u_0)$

$$x_e = -(A + BK)^{-1}(B_r r + Bw_f) \quad (16)$$

where r and w_f are constant signals. This equilibrium actually belongs to $S(K, u_0)$ as soon as

$$| -K(A + BK)^{-1}(B_r r + Bw_f) | \leq u_0$$

which corresponds to impose a condition on the admissible signals r and w_f .

Moreover, if one examines the structure of matrices A , B_r and B one can write, with $K_c = [K_1 \ K_2 \ K_3]$ and $\tilde{k}_{10} = k_{10} + k_{12} + k_{13}$:

$$\begin{bmatrix} -k_{e0} \frac{k_{e0}}{V_1} & 0 & 0 & 0 \\ K_1 & -\tilde{k}_{10} + K_2 & K_3 & k_{21} & k_{31} \\ 1 & 0 & 0 & 0 & 0 \\ 0 & k_{12} & 0 & -k_{12} & 0 \\ 0 & k_{13} & 0 & 0 & -k_{13} \end{bmatrix} \begin{bmatrix} e \\ x_{f2} \\ \xi \\ x_{s1} \\ x_{s2} \end{bmatrix} = \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} r + \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} w_f \quad (17)$$

The nominal closed-loop equilibrium point is defined as follows:

$$x_e = \begin{bmatrix} 0 \\ V_1 k_{bis} \\ \frac{k_{10} - K_2}{K_3} V_1 k_{bis} \\ \frac{k_{12}}{k_{21}} V_1 k_{bis} \\ \frac{k_{13}}{k_{31}} V_1 k_{bis} \end{bmatrix} r + \begin{bmatrix} 0 \\ 0 \\ \frac{1}{K_3} \\ 0 \\ 0 \end{bmatrix} w_f \quad (18)$$

By noting the structure of K and K_c , from (18) it follows that

$$Kx_e = k_{10}V_1k_{bis}r + w_f$$

Hence, the nominal closed-loop equilibrium point belongs to the region of linearity $S(K, u_0)$ as soon as

$$\begin{bmatrix} r \\ w_f \end{bmatrix}' \begin{bmatrix} k_{10}V_1k_{bis} \\ 1 \end{bmatrix}' \frac{1}{u_0^2} \begin{bmatrix} k_{10}V_1k_{bis} \\ 1 \end{bmatrix} \begin{bmatrix} r \\ w_f \end{bmatrix} \leq 1 \quad (19)$$

As expected, the integral action induces a perfect reference tracking since it is ensured that $e(t) = 0$, as soon as $x_e \in S(K, u_0)$, that is, if r and w_f satisfy relation (19).

3.3 Problem formulation

Let \mathcal{X}_0 be the set of admissible initial conditions, \mathcal{R}_0 the set of references and \mathcal{W}_0 the set of admissible perturbations w_f of system (13). The problem to be solved can be summarized as follows:

Problem 1. Design the state-feedback gain K_c and characterize the sets \mathcal{X}_0 , \mathcal{R}_0 and \mathcal{W}_0 , such that, $\forall x(0) \in \mathcal{X}_0$, $\forall r \in \mathcal{R}_0$ and $w_f \in \mathcal{W}_0$, the equilibrium point $x_e \in S(K_c, u_0)$ is locally asymptotically stable, $y_f(t) \rightarrow r$ when $t \rightarrow \infty$, and \mathcal{X}_0 is an invariant domain in which the trajectories of the closed-loop saturated system (13) remain confined, despite the saturation, perturbations and uncertainties.

4. CONTROLLER DESIGN

Now, we are in position to state the main result to address Problem 1.

Proposition 1. If there exist four symmetric positive definite matrices $W_f \in \mathbb{R}^{(n_f+1) \times (n_f+1)}$, $W_s \in \mathbb{R}^{n_s \times n_s}$, $Q_r \in \mathbb{R}$, $Q_w \in \mathbb{R}$, a diagonal positive definite matrix $S \in \mathbb{R}$, two matrices $Y \in \mathbb{R}^{1 \times (n_f+1)}$ and $Z \in \mathbb{R}^{1 \times (n_f+1)}$, and positive scalars $\tau_1, \tau_2, \tau_3, \tau_4, \tau_5, \tau_6, \tau_7, \tau_8, \delta_f$ and δ_s such that²

$$\begin{bmatrix} He(A_{fe}^{[i]}W_f + B_{fe}Y) + \tau_1W_f & \star & \star & \star & \star \\ SB'_{fe} - Z & -2S & \star & \star & \star \\ W_s A_{fse}^{[i]'} & 0 & -\tau_2W_s & \star & \star \\ B'_{re} & 0 & 0 & -\tau_3Q_r & \star \\ B'_{fe} & 0 & 0 & 0 & -\tau_4Q_w \end{bmatrix} < 0 \quad (20)$$

$$\begin{bmatrix} He(A_s^{[i]}W_s) + \tau_5W_s & \star \\ W_f A_{sfe}^{[i]'} & -\tau_6W_f \end{bmatrix} < 0 \quad (21)$$

$$\begin{bmatrix} W_f & \star \\ Y - Z & \delta_f u_0^2 \end{bmatrix} \geq 0 \quad (22)$$

² $\bullet^{[i]}$ corresponds to each of the N vertices which describe the polytopic uncertain matrices issued from matrix A defined in (3).

$$\begin{bmatrix} -\tau_7Q_r & \star & \star \\ 0 & -\tau_8Q_w & \star \\ k_{10}^{[i]}V_1k_{bis} & 1 & -u_0^2 \end{bmatrix} \leq 0 \quad (23)$$

$$-\tau_1\delta_s + (\tau_2 + \tau_3 + \tau_4)\delta_f < 0 \quad (24)$$

$$-\tau_5\delta_f + \tau_6\delta_s < 0 \quad (25)$$

$$\tau_7 + \tau_8 - \delta_s < 0 \quad (26)$$

then the controller $K_c = YW_f^{-1}$ is such that for any reference $r \in \mathcal{R}_0 = \{r \in \mathbb{R}; r'Q_r r \leq \delta_s^{-1}\}$, disturbance $w_f \in \mathcal{W}_0 = \{w_f \in \mathbb{R}^m; w_f'Q_w w_f \leq \delta_s^{-1}\}$, $x_{fe}(0) \in \mathcal{X}_0^f = \{x_{fe} \in \mathbb{R}^{n_f+1}; x_{fe}'W_f^{-1}x_{fe} \leq \delta_f^{-1}\}$ and $x_s(0) \in \mathcal{X}_0^s = \{x_s \in \mathbb{R}^{n_s}; x_s'W_s^{-1}x_s \leq \delta_s^{-1}\}$, the trajectories of the closed-loop saturated system (13) do not leave the ellipsoidal domain $\mathcal{X}_0 = \mathcal{X}_0^f \times \mathcal{X}_0^s$.

Proof. The proof involves Lyapunov-based arguments, considering quadratic Lyapunov functions $V(x_{fe}) = x_{fe}'W_f^{-1}x_{fe}$ and $V(x_s) = x_s'W_s^{-1}x_s$, with symmetric positive definite matrices $W_f \in \mathbb{R}^{(n_f+1) \times (n_f+1)}$ and $W_s \in \mathbb{R}^{n_s \times n_s}$. Also, to deal with the dead-zone nonlinearity $\phi(Kx) = \phi(K_c x_{fe})$, it takes advantage of the modified sector condition (Tarbouriech et al. (2011))

$$\phi(K_c x_{fe})'T(\phi(K_c x_{fe}) + Gx_{fe}) \leq 0,$$

verified with a positive diagonal matrix T for any x_{fe} belonging to the polyhedron $S(|K_c - G|, u_0)$ defined by:

$$S(|K_c - G|, u_0) = \{x_{fe} \in \mathbb{R}^{n_f+1}; -u_0 \leq (K_c - G)x_{fe} \leq u_0\}.$$

Then to prove that the trajectories of the closed-loop system (11) remain confined in $\mathcal{X}_0 = \mathcal{X}_0^f \times \mathcal{X}_0^s$ for all references $r \in \mathcal{R}_0$ and all disturbance $w_f \in \mathcal{W}_0$, one has to prove that, along the trajectories of the closed-loop saturated system (13), one gets: $\dot{V}(x_{fe}) < -\alpha(V(x_{fe}))$, α being a \mathcal{K} -function, for any x_{fe} such that $x_{fe}'W_f^{-1}x_{fe} > \delta_f^{-1}$, for any $r \in \mathcal{R}_0$, any $w_f \in \mathcal{W}_0$ and any $x_s \in \mathcal{X}_0^s$. Thanks to the use of the S-procedure (Boyd et al. (1994)) and the modified sector condition, this condition on the time derivative of $V(x_{fe})$ is satisfied, with $\tau_i, i = 1, \dots, 4$, if

$$\begin{aligned} \dot{V}(x_{fe}) + \tau_1(x_{fe}'W_f^{-1}x_{fe} - \delta_f^{-1}) + \tau_2(\delta_s^{-1} - x_s'W_s^{-1}x_s) \\ + \tau_3(\delta_s^{-1} - r'Q_r r) + \tau_4(\delta_s^{-1} - w_f'Q_w w_f) \\ - 2\phi(K_c x_{fe})'T(\phi(K_c x_{fe}) + Gx_{fe}) < 0 \end{aligned} \quad (27)$$

which is satisfied as long as (20) and (24) are satisfied, and $\mathcal{X}_0^f \subseteq S(|K_c - G|, u_0)$. This latter condition is ensured with the inequality (22), by using the change of variables $K_c W_f = Y$ and $G W_f = Z$. Then one can prove that there exists a small enough positive scalar ϵ allowing to select the \mathcal{K} -function $\alpha(V(x_{fe}))$ as $\epsilon x_{fe}'x_{fe}$. Therefore, the satisfaction of (20), (22) and (24) guarantees that x_{fe} remains confined in \mathcal{X}_0^f for the uncertain closed-loop fast system, for any $r \in \mathcal{R}_0$, $w_f \in \mathcal{W}_0$ and any $x_s \in \mathcal{X}_0^s$. Note also that, thanks to the polytopic representation of the uncertain matrix A (and subsystems A_{fe}, A_{fse}, B_{re}), the inequality (20) holds at each vertex i . That concludes the first part of the proof.

Similarly, the satisfaction of relations (21) et (25) ensures the invariance of the ellipsoid \mathcal{X}_0^s for the uncertain slow system, for any $x_{fe} \in \mathcal{X}_0^f$.

Finally, the satisfaction of relations (23) and (26) ensures that relation (19) holds for any $r \in \mathcal{R}_0$ and $w_f \in \mathcal{W}_0$. Therefore, the equilibrium point belongs to the region of linearity (as discussed in Section 3.2). \square

The approach of splitting the system into fast and slow subsystems and considering the slow subsystem as a disturbance of the fast one is interesting in the sense that it helps focusing the study on the subsystem of interest allowing to satisfy some performances that we could not guarantee with the global system considering the multi-time scale dynamics problem. However, this approach induces some conservatism by the fact that x_s is manipulated as a disturbance, which can then evolve independently of x_f (or x_{fe}), due to the manner to build the set \mathcal{X}_0 (i.e. $\mathcal{X}_0^f \times \mathcal{X}_0^s$). Therefore the estimations of \mathcal{X}_0 and \mathcal{R}_0 are conservative by construction. Then, once the controller has been computed, one can consider the analysis of the full system to get a better estimation of admissible \mathcal{X}_0 and \mathcal{R}_0 , considering the full closed-loop saturated system (13). The following proposition gives conditions to address the analysis problem.

Proposition 2. Given the controller gain $K = [K_c \ 0_{1 \times n_s}]$, if there exist three symmetric positive definite matrices $W \in \mathbb{R}^{n \times n}$, $Q_r \in \mathbb{R}$, $Q_w \in \mathbb{R}$, a diagonal positive definite matrix $S \in \mathbb{R}$, a matrix $Z \in \mathbb{R}^{1 \times n}$, and positive scalars³ $\tau_1, \tau_3, \tau_4, \tau_7, \tau_8, \delta_s$ and η such that relation (23) and the following hold

$$\begin{bmatrix} He(A^{[2]}W + BKW) + \tau_1 W & \star & \star & \star \\ SB' - Z & -2S & \star & \star \\ B_r^{[2]} & 0 & -\tau_3 Q_r & \star \\ B & 0 & 0 & -\tau_4 Q_w \end{bmatrix} < 0 \quad (28)$$

$$\begin{bmatrix} W & \star \\ KW - Z & \eta u_{0(j)}^2 \end{bmatrix} \geq 0 \quad (29)$$

$$\begin{bmatrix} -\tau_7 Q_r & \star & \star \\ 0 & -\tau_8 Q_w & \star \\ k_{10}^{[2]} V_1 k_{bis} & 1 & -u_0^2 \end{bmatrix} \leq 0 \quad (30)$$

$$-\tau_1 \delta_s + (\tau_3 + \tau_4) \eta < 0 \quad (31)$$

$$\tau_7 + \tau_8 - \delta_s < 0 \quad (32)$$

then for any reference $r \in \mathcal{R}_0 = \{r \in \mathbb{R}; r' Q_r r \leq \delta_s^{-1}\}$, disturbance $w_f \in \mathcal{W}_0 = \{w_f \in \mathbb{R}^m; w_f' Q_w w_f \leq \delta_s^{-1}\}$, the trajectories of the closed-loop saturated system (13) do not leave the ellipsoidal domain $\mathcal{X}_0 = \{x \in \mathbb{R}^n; x' W^{-1} x \leq \eta^{-1}\}$.

Proof. The same arguments as in the proof of Proposition 1 can be invoked when manipulating the full system (13) with given controller gain K . \square

³ To simplify the comparison with Proposition 1, we keep the same notations for scalars τ_i .

5. NUMERICAL EXAMPLE

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

Param	k_{10}	k_{21}	k_{12}
interval	[0.2497, 0.8982]	[0.2066, 0.4876]	[0.0655, 0.0720]

Table 2. Uncertain parameters intervals

The controller is designed with the objective of accelerating by twice the closed-loop dynamics, which is guaranteed by setting $\tau_1 = 1.8$. A solution is computed by solving the conditions of Proposition 1 with an optimization criterion set as:

$$\begin{aligned} & \min \text{Trace}(Q_r) + \delta_s \\ & \text{under conditions (20)-(26)} \end{aligned}$$

With $\tau_2 = 2$, $\tau_3 = \tau_4 = 0.001$, $\tau_5 = 0.0006$, $\tau_6 = 0.0005$, $\tau_7 = \tau_8 = 0.01$, one obtains the control gain:

$$K_c = [-169.4040 \quad -10.6163 \quad -136.0120]$$

To illustrate the performance of this controller, it is applied on 7 adult patients chosen in the range considered above to design the controller and whose characteristics are detailed in Table 3.

	Age (yr)	size (cm)	weight (kg)	sex
1	20	140	38	F
2	43	155	55	F
3	52	160	65	M
4	35	170	73	F
4	56	185	84	M
6	32	200	85	M
7	70	177	77	M

Table 3. Patient dataset

For the simulations, the patients are initially awake ($y_{bis} = 100$). First, before to close the loop, an initial bolus is administered to mimic the medical practice. Typically, an optimal control strategy could be applied for this induction phase (Zabi et al. (2017)). Here, one simply considers a bolus of 60 mg (120 mg/min during 30 seconds). Then the loop is closed after 1 minute. Figures 1 and 2 report the output and input responses for all these 7 patients. It may be checked that the output closed-loop behavior is almost the same. On the other hand, the influence of the patient is visible on the input behavior allowing to track the BIS, exhibiting a good robustness of the designed controller with respect to the considered uncertain parameters.

6. CONCLUSION

The tracking problem of a constant BIS reference during anesthesia has been addressed in this paper taking into account 1) control input saturation, 2) patient uncertainty and 3) combination of fast and slow dynamics inherent to such a system. LMI conditions have been established to compute a state feedback involving an integral action in order to ensure a perfect output tracking. These conditions guarantee that the trajectories of the closed-loop system remain confined in an invariant ellipsoidal set, provided

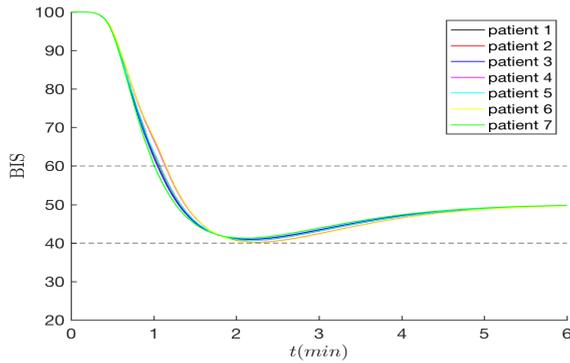


Fig. 1. BIS reference tracking for 7 adult patients.

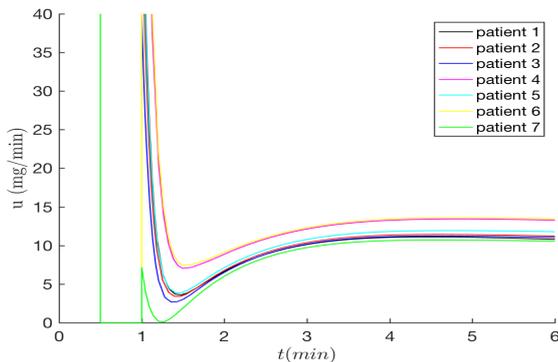


Fig. 2. Infusion rate of propofol during BIS reference tracking for 7 adult patients.

that the reference signal belongs to a certain set. The theoretical conditions have been numerically tested on a set of patients as a proof of principle.

Several directions of research could be investigated, in particular to take into account the fact that the concentration of drug in the central compartment (x_{f2}) is not easily accessible. It would then be pertinent to add an observer to the controller scheme, or to extend the results to the dynamic output-feedback control design. Moreover, more realistic uncertainty descriptions should be considered in the future, in particular on the pharmacodynamic model.

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