HAL
open science

Controller design for analgesia with quantized pupil size variation output and saturating infusion rate

Saïd Zabi, Isabelle Queinnec, Sophie Tarbouriech, Michel Mazerolles

To cite this version:

Saïd Zabi, Isabelle Queinnec, Sophie Tarbouriech, Michel Mazerolles. Controller design for analgesia with quantized pupil size variation output and saturating infusion rate. 10th IFAC Symposium on Nonlinear Control Systems (NOLCOS), IFAC, Aug 2016, Monterey, United States. pp.760-765, 10.1016/j.ifacol.2016.10.255 . hal-01474499

HAL Id: hal-01474499

https://laas.hal.science/hal-01474499v1

Submitted on 22 Feb 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Controller design for analgesia with quantized pupil size variation output and saturating infusion rate

Said Zabi * **Isabelle Queinnec** * **Sophie Tarbouriech** *
Michel Mazerolles **

* *LAAS-CNRS, Université de Toulouse, CNRS, Toulouse, France.*
szabi,queinnec,tarbour@laas.fr
** *Département d'anesthésie-réanimation, CHU Toulouse, France,*
mazerolles.m@chu-toulouse.fr

Abstract: This paper proposes a strategy for the design of a dynamic output-feedback controller for analgesia taking into account the saturation of the input and the quantization of the output. Besides that, the design of this controller takes into account the multiple time scale dynamics in the analgesia model, accelerates the fast dynamics and establishes global stability. The control design is cast into a two-step strategy. The controller is first designed for the fast system and the stability analysis is then performed on the full model to evaluate domains of safe behavior.

Keywords: Analgesia, saturated control, quantification, pupil size variation, multiple time scale.

1. INTRODUCTION

Although an adequate hypnotic state (anesthesia) prevents the patient from recalling noxious stimulus, the pain they cause is still felt and viewed via some variations on haemodynamics, respiration, hormonal secretion, etc. This can be extenuated by analgesic drugs which compromise the sympathetic and parasympathetic nervous system. Based on those phenomena, several studies have been concerned with the selection of reliable indicators. [De Jonckheere et al. (2012)], [Balocchi et al. (2005)] proposed an evaluation of the depth of analgesia by analyzing the heart rate variability and introduced the ANI (for Autonomic Nervous Index). Blood pressure, grimaces, electrocardiogram (EEG), the difference of entropy and other indicators were also proposed in [Gentilini et al. (2002)], [Mathews et al. (2007)], [Huiku et al. (2007)], [Ushiyama et al. (2008)]. In this work we use the response of the pupil as an indicator, being shown that its area variates according to nociceptive stimulation [Mazerolles (2009)]. Actually, [Barvais et al. (2003)] showed that the pupil response to a painful stimulus is a better indicator of the effect site remifentanil concentration than haemodynamics or BIS measurements.

Control of analgesia has been mainly devoted to hypnosis, including the presence of saturation and associated windup effects [Zhusubaliyev et al. (2014)], [van Heusden et al. (2014)]. A few works have concerned analgesia using PID-based feedback control strategies [Soltesz et al. (2011)] or model predictive control [Gentilini et al. (2002)]. As many biological systems, the closed-loop controller design of analgesia should consider some physical aspects such as patient variability, positivity constraints, output measurement availability, ... Among these aspects, an important peculiarity is the presence of multiple time scales in the dynamics. Indeed, the dynamics of the evolution of the drug in the patient's body is usually described by a pharmacokinetic model with multiple time scales. We reformulate the problem by separating fast and slow dynamics in order to reduce the control design problem to that one of the fast subsystem (the DoA being directly linked to the states of the fast subsystem) before to analyze the global system in a second step. Moreover, one considers a pupillary sensor as the output of the controlled system. It is a quantized signal corresponding to the smallest magnitude of a stimulus that induces a significant dilatation of the pupil. The global goal is then to control the DoA 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 remifentanil) intravenously. Therefore, the framework considered here is that one of quantized [Tarbouriech and Gouaisbaut (2012)] and saturated systems [Tarbouriech et al. (2011)].

The main contribution of the paper resides in the approach proposed for the design of a dynamic output-feedback controller of the same order as the fast subsystem through matrix inequalities conditions taking into account the quantized nature of the output and the saturation of the input.

2. MODELLING ASPECTS

2.1 The patient model

The model used to describe the circulation of drugs in a patient's body, known as Pharmacokinetic/Pharmacodynamic (PK/PD) model, is based on a classical three-compartment model [Derendorf and Meibohm (1999)]. It describes the distribution of the drugs between three compartments (blood, muscles and fat). The effect of drugs on the patient is expressed throughout the effect site, which represents the action of drugs on the brain and is related to the

concentration in the central compartment through a first order dynamic [Beck (2015)].

In open loop, each constant input rate of the analgesic drug corresponds to a unique equilibrium point [Zabi et al. (2015)]. Thus the following model represents the patient with any desired equilibrium point (u_e, x_e) taken as origin

$$\dot{x}_{an}(t) = A_{an}x_{an}(t) + B_{an}u_{an}(t) \tag{1}$$

with

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

$$B_{an} = [\,1\ 0\ 0\ 0\,]'$$

where, with respect to (u_e, x_e), $x_{an} = [x_1\ x_2\ x_3\ x_4]'$, $x_1(t)$, $x_2(t)$, $x_3(t)$ are the error of masses in grams of the analgesic in the different compartments, $x_4(t)$ is the error of the effect site concentration and $u_{an}(t)$ is the error of the infusion rate in g/min of the analgesic. Among various existing models, which express the model parameters as functions of the patient characteristics (weight, age, height, ...), we choose for the case of analgesic drugs the model of Minto [Minto et al. (1997)] to define typical patients for numerical simulations.

Remark 1. The constraints of positivity on the real system are as follows

$$x_{an} \geq -x_e \quad ; \quad u_{an} \geq -u_e \tag{2}$$

2.2 The quantized measurement

The pupil size variation in reaction to an electrical pulse of given intensity is inversely proportional to the effect site concentration of drug. In [Zabi et al. (2016)], a second order state space model is proposed to estimate the pupil size variation in % with respect to an electrical stimulation and function of the site-effect drug concentration. The smallest magnitude of stimuli that induces a significant pupil size variation (the DoA) can then be expressed by the output function $y = h(x_4)$ [Zabi et al. (2016)]. Actually, this information is only available as a multiple of a constant since it is obtained by means of successive increasing impulsive pulses. By linearizing at the desired equilibrium (u_e, x_e), one can express the output equation

$$y = q(Cx_{an}) \tag{3}$$

with $C = [\,0\ 0\ 0\ c_4\,]$. $q(.)$ is the uniform quantizer, having as quantization error bound $\Delta > 0$, defined by [Ferrante et al. (2015)]

$$q_\Delta : \begin{cases} \mathbb{R}^p \to \Delta\mathbb{Z}^p \\ z \mapsto \Delta sign(z) \left\lfloor \dfrac{|z|}{\Delta} \right\rfloor \end{cases} \tag{4}$$

2.3 Multiplicity of dynamics

Regardless of patient under consideration, the dynamics of metabolism and circulation of the analgesic drug 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. In this case, if one treats the synthesis problem directly for system (1), the synthesis controller would result in accelerating slow dynamics, while the output that we want to control is influenced mainly by the fast dynamics.

Thus, in the following, thanks to the particular structure of the system, we 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 are influenced only by the state of the fast subsystem.

Let us denote $x_f = [x_1\ x_4]' \in \mathbb{R}^2$ the fast state vector, $x_s = [x_2\ x_3]' \in \mathbb{R}^2$ the slow state vector and $u = u_{an}$. System (1) can be written as follows:

$$\dot{x}_f = A_f x_f + B_f sat(u) + A_{fs}x_s \tag{5a}$$
$$\dot{x}_s = A_{sf}x_f + A_s x_s \tag{5b}$$
$$y_f = q(C_f x_f) \tag{5c}$$

3. GENERAL PROBLEM FORMULATION

Consider the following generic continuous-time linear system with quantized sensor and saturated input

$$\begin{aligned} \dot{x}_p &= A_p x_p + B_p sat(u) \\ y &= q(C_p x_p) \end{aligned} \tag{6}$$

where $x_p \in \mathbb{R}^n, u \in \mathbb{R}^m, y \in \mathbb{R}^p$ are respectively the state, the input and the measured output of the plant. $q(.)$ is the uniform quantizer defined in (4) and $sat(.)$ denotes the vector-valued saturation function defined as $sat(u_{(i)}) = sign(u_{(i)})min\{u_{0(i)}, |u_{(i)}|\}$, $i = 1, \ldots, m$, $u_{0(i)} > 0$ being the level of saturation of the $i-$th component of u. We want to design the following $n-$order dynamic output-feedback stabilizing controller for (6):

$$\begin{aligned} \dot{x}_c &= A_c x_c + B_c u_c + E_c \phi(y_c) \\ y_c &= C_c x_c + D_c u_c \end{aligned} \tag{7}$$

where $x_c \in \mathbb{R}^n$, $u_c \in \mathbb{R}^p$, $y_c \in \mathbb{R}^m$ are respectively the state, the input and the output of the controller. Denoting the dead-zone element $\phi(y_c) = sat(y_c) - y_c \in \mathbb{R}^m$, $E_c\phi(y_c)$ is a static anti-windup term introduced to alleviate undesirable effects caused by the actuator saturation [Zaccarian and Teel (2011), Tarbouriech et al. (2011)]. Matrices A_c, B_c, C_c, D_c and E_c are constant matrices of appropriate dimensions to be designed. The interconnection between the plant (6) and the controller (7) by setting $u = y_c, u_c = y$, yields the following closed-loop system:

$$\begin{aligned} \dot{x}_p &= A_p x_p + B_p sat(C_c x_c + D_c q(C_p x_p)) \\ \dot{x}_c &= A_c x_c + B_c q(C_p x_p) + E_c \phi(C_c x_c + D_c q(C_p x_p)) \end{aligned} \tag{8}$$

By defining the augmented vector state $x = [x_p'\ x_c']' \in \mathbb{R}^{2n}$ and by defining $\psi(z) = q(z) - z$, the closed-loop system (8) reads:

$$\dot{x} = Ax + B_\phi \phi(Kx + D_c\psi(Cx)) + B_\psi \psi(Cx) \tag{9}$$

with

$$A = \begin{bmatrix} A_p + B_p D_c C_p & B_p C_c \\ B_c C_p & A_c \end{bmatrix}; \quad B_\phi = \begin{bmatrix} B_p \\ E_c \end{bmatrix}$$

$$K = [\,D_c C_p\ C_c\,]; \quad C = [\,C_p\ 0\,]; \quad B_\psi = \begin{bmatrix} B_p D_c \\ B_c \end{bmatrix}.$$

Remark 2. Due to the presence of the uniform quantizer, there is no guarantee on the existence of solutions to the

discontinuous equation (8) in the classical sense [Cortes (2008)]. To simplify the development of the result below, we suppose that the Caratheodory solutions to system (8) exist as in [Tarbouriech and Gouaisbaut (2012)]. More general solutions as Krasovskii solutions could be studied by using differential inclusions [Ferrante et al. (2015)].

The problem we intend to solve can then be formulated as follows:

Problem 1. Design A_c, B_c, C_c, D_c, E_c and characterize two sets $\mathcal{A}_0$, $\mathcal{A}_\infty$ such that for every initial conditions $x(0)$ belonging to $\mathcal{A}_0 \setminus \mathcal{A}_\infty$, the resulting trajectories of system (9) converge toward $\mathcal{A}_\infty$.

Depending on the stability property of the open-loop matrix A_p, due to the presence of the input saturation, Problem 1 can be turned in a global context. In this case, the set $\mathcal{A}_0$ corresponds to the whole state space $\mathbb{R}^{2n}$ and $\mathcal{A}_\infty$ is a global attractor for system (9).

4. MATHEMATICAL PRELIMINARIES

4.1 Preliminary lemmas

The closed-loop system (9) contains nested non-linearities since ϕ depends on ψ. To solve Problem 1, we exploit the sector conditions both for ψ as presented in [Ferrante et al. (2015)] and for ϕ as given in [Tarbouriech et al. (2006)]. Let us recall these conditions.

Lemma 1. [Ferrante et al. (2015)] Let $z \in \mathbb{R}^p$, and let $S_1, S_2 \in \mathbb{R}^{p\times p}$ be diagonal positive definite matrices. Then the pair $(\psi(z), z)$ satisfies the following conditions:

$$\psi'(z)S_1\psi(z) - trace(S_1)\Delta^2 \leq 0 \tag{10}$$

$$\psi'(z)S_2(\psi(z) + z) \leq 0 \tag{11}$$

Lemma 2. [Tarbouriech et al. (2006)] Considering a matrix $G \in \mathbb{R}^{m\times 2n}$, the non-linearity $\phi(y_c)$ satisfies

$$\phi(y_c)'T(\phi(y_c) + D_c\psi(\tilde{C}x) + Gx) \leq 0 \tag{12}$$

for any diagonal positive matrix $T \in \mathbb{R}^{m\times m}$ if $x \in \mathcal{S}(u_0)$ with

$$\mathcal{S}(u_0) = \left\{ \begin{array}{l} x \in \mathbb{R}^n; \forall i \in \{1, ..., m\}, \\ \quad -u_{0(i)} \leq (K_{(i)} - G_{(i)})x \leq u_{0(i)} \end{array} \right\} \tag{13}$$

4.2 Stability analysis results

Conditions for stability analysis purpose of system (8) or (9) can be proposed based on the use of Lemmas 1 and 2.

Proposition 1. Given A_c, B_c, C_c, D_c, E_c. Assume there exist a symmetric positive definite matrix $P \in \mathbb{R}^{2n\times 2n}$, three diagonal positive definite matrices $S_1, S_2 \in \mathbb{R}^{p\times p}, T \in \mathbb{R}^{m\times m}$, a matrix $G \in \mathbb{R}^{m\times 2n}$ and positive scalars τ_1, τ_2, η such that [1]

$$\begin{bmatrix} He(PA) + (\tau_1 - \tau_2)P & PB_\psi - C'S_2 & PB_\phi - G'T \\ \star & -S_1 - 2S_2 & -D_c'T \\ \star & \star & -2T \end{bmatrix} < 0 \tag{14}$$

[1] In symmetric matrices, the notation $\star$ stands for symmetric blocks and $He(A) = A' + A$.

$$\begin{bmatrix} P & K'_{(i)} - G'_{(i)} \\ \star & \eta u_{0(i)}^2 \end{bmatrix} \geq 0 \; i = 1, ..., m. \tag{15}$$

$$\eta\Delta^2 trace(S_1) - \tau_1\eta + \tau_2 \leq 0 \tag{16}$$

$$\eta \leq 1 \tag{17}$$

Then by defining the sets

$$\mathcal{A}_0 = \mathcal{E}(P, \eta) := \{x \in \mathbb{R}^{2n} : x'Px \leq \eta^{-1}\} \tag{18a}$$

$$\mathcal{A}_\infty = \mathcal{E}(P) := \{x \in \mathbb{R}^{2n} : x'Px \leq 1\} \tag{18b}$$

it follows that for any $x(0) \in \mathcal{A}_0 \setminus \mathcal{A}_\infty$ the closed-loop trajectories converge to $\mathcal{A}_\infty$.

The proof is postponed in Section 8.

If matrix A_p is Hurwitz, the global asymptotic stability of system (8) can be addressed through the following corollary

Corollary 1. Given A_c, B_c, C_c, D_c, E_c. Assume there exist a symmetric positive definite matrix $P \in \mathbb{R}^{2n\times 2n}$, three diagonal positive definite matrices $S_1, S_2 \in \mathbb{R}^{p\times p}, T \in \mathbb{R}^{m\times m}$ and a positive scalar τ_1 such that

$$\begin{bmatrix} He(PA) + \tau_1 P & PB_\psi - C'S_2 & PB_\phi - K'T \\ \star & -S_1 - 2S_2 & -D_c'T \\ \star & \star & -2T \end{bmatrix} < 0 \tag{19}$$

$$\Delta^2 trace(S_1) - \tau_1 \leq 0 \tag{20}$$

Then for any $x(0) \in \mathbb{R}^{2n} \setminus \mathcal{A}_\infty$ with $\mathcal{A}_\infty$ defined as in (18b), the closed-loop trajectories converge toward $\mathcal{A}_\infty$.

Proof: It readily follows the proof of Proposition 1 by considering Lemma 1 in global case, that is by setting $G = K$. Then, in this case, one wants to prove that $\dot{V} < -\alpha(V(x))$, α being a $\mathcal{K}$-function, for any x such that $x'Px \geq 1$.

4.3 Control design results

To address Problem 1 and to remove products between decision variables, in particular those involving A_c, B_c, C_c, D_c, E_c and P, we use similar congruence transformations as proposed in [Scherer et al. (1997)]. The following result, for which the proof is postponed in Section 8 can then be stated.

Proposition 2. If there exist two symmetric positive definite matrices $X, Y \in \mathbb{R}^{n\times n}$, three diagonal positive definite matrices $S_1, S_2 \in \mathbb{R}^{p\times p}, S \in \mathbb{R}^{m\times m}$, matrices $W \in \mathbb{R}^{n\times n}$, $R \in \mathbb{R}^{n\times m}$, $L \in \mathbb{R}^{n\times p}$, $M \in \mathbb{R}^{m\times n}$, $N \in \mathbb{R}^{m\times p}$, $Z \in \mathbb{R}^{m\times n}$, $Z_1 \in \mathbb{R}^{m\times n}$ and positive scalars τ_1, τ_2, η such that relations (16) and (17) hold and

$$\begin{bmatrix} He(H_1) + (\tau_1 - \tau_2)H_2 & H_3 & H_4 \\ \star & -S_1 - 2S_2 & -N' \\ \star & \star & -2S \end{bmatrix} < 0 \tag{21}$$

$$\begin{bmatrix} H_2 & H_5 \\ \star & \eta u_{0(i)}^2 \end{bmatrix} \geq 0 \; i = 1, ..., m \tag{22}$$

where

$$H_1 = \begin{bmatrix} A_pY + B_pM & A_p + B_pNC_p \\ W & XA_p + LC_p \end{bmatrix}, H_2 = \begin{bmatrix} Y & I \\ \star & X \end{bmatrix},$$

$$H_3 = \begin{bmatrix} B_pN - YC_p'S_2 \\ L - C_p'S_2 \end{bmatrix}, H_4 = \begin{bmatrix} B_pS - Z' \\ R - Z_1' \end{bmatrix}, \quad (23)$$

$$H_5 = \begin{bmatrix} M_{(i)}{}' - Z_{(i)}{}' \\ C_p'N_{(i)}{}' - Z_{1(i)}{}' \end{bmatrix}, \quad i = 1, ..., m.$$

Then

$$\begin{aligned} E_c &= U^{-1}(R - XB_pS)S^{-1} \\ D_c &= N \\ C_c &= (M - NC_pY)(V')^{-1} \\ B_c &= U^{-1}(L - XB_pN) \\ A_c &= U^{-1}(W - XA_pY - XB_pM - UB_cC_pY)(V')^{-1} \end{aligned}$$

and $\mathcal{A}_0 = \mathcal{E}(P, \eta)$, $\mathcal{A}_\infty = \mathcal{E}(P)$, where $U, V \in \mathbb{R}^n$ are any nonsingular matrices such that $UV' = I - XY$ and

$$P = \begin{bmatrix} X & U \\ U' & \hat{X} \end{bmatrix} \text{ with } \hat{X} = U'(X - Y^{-1})^{-1})U \quad (24)$$

are solution to problem 1.

Remark 3. Relations of Proposition 2 yet involve some products between decision variables, in particular in the terms $(\tau_1 - \tau_2)H_2$, $YC_f'S_2$ in (21), or still $\eta\tau_1$, $\eta\,\mathrm{trace}(S_1)$ in (16). Nevertheless, by fixing τ_1, τ_2, τ_3, S_1 and S_2, the relations become linear. They can be, for example, selected by performing a grid search over a certain interval.

A similar result can be provided in the global context of Corollary 1.

Corollary 2. Suppose there exist two symmetric positive definite matrices $X, Y \in \mathbb{R}^{n\times n}$, three diagonal positive definite matrices $S_1, S_2 \in \mathbb{R}^{p\times p}, S \in \mathbb{R}^{m\times m}$, matrices $W \in \mathbb{R}^{n\times n}$, $R \in \mathbb{R}^{n\times m}$, $L \in \mathbb{R}^{n\times p}$, $M \in \mathbb{R}^{m\times n}$, $N \in \mathbb{R}^{m\times p}$ and a positive scalar τ_1 such that relation (20) holds and

$$\begin{bmatrix} He(H_1) + \tau_1 H_2 & H_3 & \tilde{H}_4 \\ \star & -S_1 - 2S_2 & -N' \\ \star & \star & -2S \end{bmatrix} < 0 \quad (25)$$

$$H_2 \geq 0 \quad (26)$$

where H_1, H_2 and H_3 are defined in (23) and

$$\tilde{H}_4 = \begin{bmatrix} B_pS - M' \\ R - C_p'N' \end{bmatrix}.$$

Then $A_c, B_c, C_c, D_c, E_c, \mathcal{A}_\infty$ as defined in Proposition 2 are solution to Problem 1 in the global case.

5. CONTROL OF ANALGESIA

5.1 Controller synthesis strategy

Due to the particular form of system (5), we apply now the results of Section 4 considering both conditions in local and global contexts. Actually, global conditions may be used since matrices A_f and A_s are Hurwitz. However, local conditions may allow to perform faster time response of the closed-loop system. Hence, we propose the following controller design procedure

1) Consider system (5a), (5c) in which the slow part is neglected, and some performance objective β for the time response through the additional condition:

$$He(H_1) + 2\beta H_2 < 0 \quad (27)$$

Proposition 2 or Corollary 2 may then be applied to design a dynamic output feedback controller of the form (7), solution to Problem 1, where A_p, B_p, C_p are replaced by A_f, B_f, C_f. In this case $n = 2, m = p = 1$. If conditions of Corollary 2 are infeasible, one can reduce β or switch to the local context and apply Proposition 2.

2) Keeping the controller designed at the above step, the closed-loop system constituted from x_f, x_c and x_s is defined by

$$\begin{aligned} \dot{z} &= \mathbf{A}z + \mathbf{B}_\phi\phi(\mathbf{K}z + D_c\psi(\mathbf{C}z)) + \mathbf{B}_\psi\psi(\mathbf{C}z) \\ y &= q(\mathbf{C}z) \end{aligned} \quad (28)$$

with $z = (x_f, x_c, x_s) \in \mathbb{R}^6$ and

$$\mathbf{A} = \begin{bmatrix} A_f + B_fD_cC_f & B_fC_c & A_{fs} \\ B_cC_f & A_c & 0 \\ A_{sf} & 0 & A_s \end{bmatrix}, \mathbf{B}_\psi = \begin{bmatrix} B_fD_c \\ B_c \\ 0 \end{bmatrix}$$

$$\mathbf{B}_\phi = \begin{bmatrix} B_f' & E_c' & 0 \end{bmatrix}', \mathbf{K} = \begin{bmatrix} D_cC_f & C_c & 0 \end{bmatrix}, \ \mathbf{C} = \begin{bmatrix} C & 0 & 0 \end{bmatrix}$$

Proposition 1 or Corollary 1 is then applied to system (28) by replacing A, B_ϕ, B_ψ, C by $\mathbf{A}$, $\mathbf{B}_\phi$, $\mathbf{B}_\psi$, $\mathbf{C}$. If the global conditions of Corollary 1 are found infeasible, one can then switch to the local context and apply Proposition 1.

5.2 Optimization issues

The optimization criterion depends on whether one is doing analysis or synthesis, in a local or a global context. In a local context, one seeks both to maximize $\mathcal{A}_0$ and minimize $\mathcal{A}_\infty$. In a global context, since $\mathcal{A}_\infty = \mathbb{R}^n$, the objective is only minimizing $\mathcal{A}_0$. The optimization criterion is then given as follow:

(1) Analysis
- Minimize $(\eta - trace(P))$ (local).
- Minimize $-trace(P)$ (global).

(2) Synthesis (Zabi et al. (2016), Ferrante et al. (2015))
- Minimize $(\eta - trace(X + Y))$ (local).
- Minimize $-trace(X + Y)$ (global).

Alternatively, in the local case, instead of minimizing $\mathcal{A}_\infty$, on can impose that it should be included in a set

$$\mathcal{P} = \{x \in \mathbb{R}^6 : |\ a_k'x| \leq 1\}$$

with $a_k' = [0\ c_4/\Delta\ \mathbf{0}_{1\times 2}\ \mathbf{0}_{1\times 2}]$. The inclusion of $\mathcal{A}_\infty$ in $\mathcal{P}$ reads

$$\begin{bmatrix} P & a_k' \\ \star & 1 \end{bmatrix} \geq 0 \quad (29)$$

and the optimization criterion becomes to minimize η, which avoids to manage the compromise between both ellipses. Note that in $\mathcal{P}$, one gets $q(C_fx_f) = C_fx_f$, i.e., $\psi = 0$.

5.3 Numerical evaluation

Let us consider a nominal patient, man, 53 years old, 77 kg, 177 cm and fix the quantization error at $\Delta = 5$. The time response performance is set as $\beta = 1$, such as to get the closed-loop system as twice faster than the open loop system dynamics. With such an objective, we could not

obtain a feasible solution to the global synthesis problem given in Corollary 2. Then considering the local controller design problem set in Proposition 2 and setting $\tau_1 = 2$, $\tau_2 = 0.002$, $\eta = 0.2, \delta = 1$ and $S_2 = 0.002$, yields the following controller

$$\left[\begin{array}{c|c} A_c & B_c \\ \hline C_c & D_c \end{array}\right] = \left[\begin{array}{cc|c} -4.75 & -19.36 & 1.10 \\ 0.09 & -1.92 & -0.11 \\ \hline 3.94 & 16.48 & -1.32 \end{array}\right], E_c = \begin{bmatrix} -1 \\ 0 \end{bmatrix}$$

Figure 1 shows the estimated sets $\mathcal{A}_0$ and $\mathcal{A}_\infty$ issued from the synthesis and analysis procedures, which exhibit the pertinence of our algorithm. Note that, in the global case where $\mathcal{A}_0$ correspond ton $\mathbb{R}^{2n}$, the physical constraints associated to the analgesia positive system guarantee that $x_p \geq -x_e$ as soon as $u \geq -u_e$. The stripes in Figure 1 correspond to this physical border from where some trajectories are initiated.

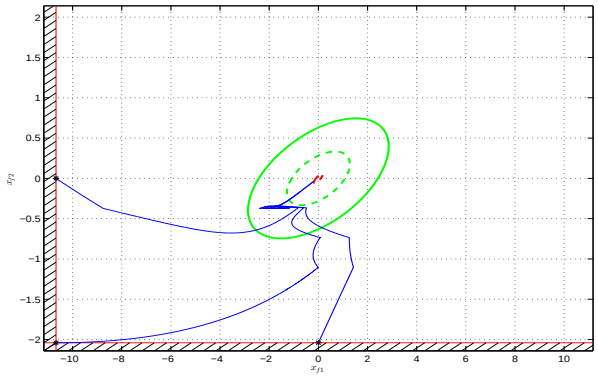

Fig. 1. $\mathcal{A}_0$ (plain) and $\mathcal{A}_\infty$ (dashed) sets projected on the fast system, synthesis (green), analysis (red) and convergent trajectories.

Figures 2 and 3 show the evolution of the DoA error and the saturated controller output for this patient.

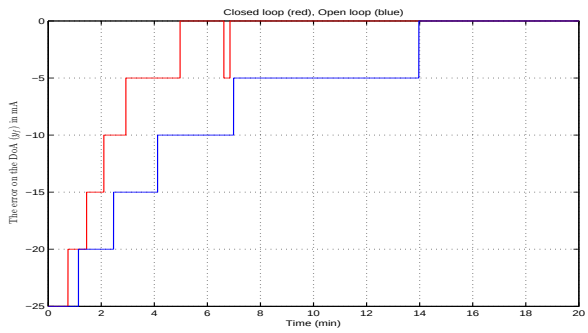

Fig. 2. DoA error in closed and open loop.

The closed-loop control is applied directly on the patient in a fully awake state. Figure 2 shows that the time response needed to achieve the target interval $[-\Delta, +\Delta]$ is less than 3 minutes which is more than twice faster compared to the open loop.

6. THANKS

This work has been partially funded by the French ANR project LimICoS grant number 12 BS03 00501.

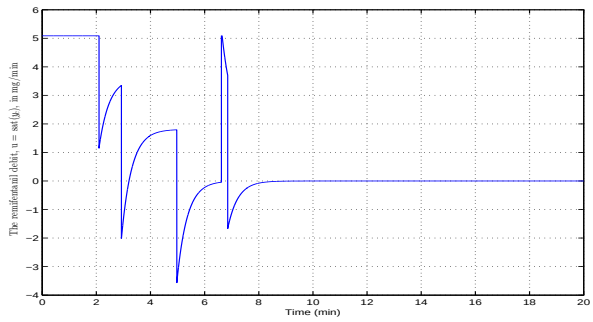

Fig. 3. Control $u = sat(y_c)$.

7. CONCLUSION

This paper proposed an approach for the synthesis of a dynamic output feedback controller for analgesia taking into account the output quantization, the input saturation with the improvement of the time response performance. The decomposition of the model into a fast and a slow systems allows to focus the control design on the fast subsystem. In order to get the performance wanted, the synthesis of the controller was done locally and in a next step the analysis showed that the results are valid in a global context. This work lets place for future works. In particular, in order to be closer to real-life anesthesia, one could manipulate a sampled output in the control scheme.

REFERENCES

Balocchi, R., Varanini, M., Menicucci, D., Santarcangelo, E., Migliorini, S., Fontani, G., and Carli, G. (2005). Heart rate variability in subjects with different hypnotic susceptibility receiving nociceptive stimulation and suggestions of analgesia. In *Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*, volume 7, 6996–6999. Shanghai, China.

Barvais, L., Engelman, E., Eba, J.M., Coussaert, E., Cantraine, F., and Kenny, G.N. (2003). Effect site concentrations of remifentanil and pupil response to noxious stimulation. *British Journal of Anaesthesia*, 91(3), 347–352.

Beck, C.L. (2015). Modeling and control of pharmacodynamics. *European Journal of Control*, 24, 33–49.

Cortes, J. (2008). Discontinuous dynamical systems. *IEEE Control Systems Magazine*, 28(3), 36–73.

De Jonckheere, J., Rommel, D., Nandrino, J., Jeanne, M., and Logier, R. (2012). Heart rate variability analysis as an index of emotion regulation processes: Interest of the Analgesia Nociception Index (ANI). In *Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*, 3432–3435. San Diego, USA.

Derendorf, H. and Meibohm, B. (1999). Modeling of pharmacokinetic / pharmacodynamic (pk/pd) relationships: Concepts and perspectives. *Pharmaceutical Research*, 16(2), 176–185.

Ferrante, F., Gouaisbaut, F., and Tarbouriech, S. (2015). Stabilization of continuous-time linear systems subject to input quantization. *Automatica*, 58, 167–172.

Gentilini, A., Schaniel, C., Morari, M., Bieniok, C., Wymann, R., and Schnider, T. (2002). A new paradigm

for the closed-loop intraoperative administration of analgesics in humans. *IEEE Transactions on Biomedical Engineering*, 49(4), 289–299.

Huiku, M., Uutela, K., van Gils, M., Korhonen, I., Kymäläinen, M., Meriläinen, P., Paloheimo, M., Rantanen, M., Takala, P., Viertiö-Oja, H., and Yli-Hankala, A. (2007). Assessment of surgical stress during general anaesthesia. *British journal of anaesthesia*, 98, 447–455.

Mathews, D.M., Cirullo, P.M., Struys, M.M.R.F., De Smet, T., Malik, R.J., Chang, C.L., and Neuman, G.G. (2007). Feasibility study for the administration of remifentanil based on the difference between response entropy and state entropy. *British Journal of Anaesthesia*, 98, 785–791.

Mazerolles, M. (2009). La pupillométrie permet-elle de mesurer la profondeur d'anesthésie ? *Praticien en Anesthésie Réanimation*, 13(2), 109–115.

Minto, C.F., Schneider, T.W., and Shafer, S.L. (1997). Pharmacokinetics and pharmacodynamics of remifentanil.Model application. *Anesthesiology*, 86(1), 24–33.

Scherer, C., Gahinet, P., and Chilali, M. (1997). Multiobjective output-feedback control via LMI optimization. *IEEE Transactions on Automatic Control*, 42, 896–911.

Soltesz, K., Hahn, J.O., Dumont, G.A., and Ansermino, J.M. (2011). Individualized PID control of depth of anesthesia based on patient model identification during the induction phase of anesthesia. In *IEEE Conference on Decision and Control*, 855–860. Orlando, USA.

Tarbouriech, S., Garcia, G., Gomes da Silva Jr, J.M., and Queinnec, I. (2011). *Stability and Stabilization of Linear Systems with Saturating Actuators*. Springer.

Tarbouriech, S. and Gouaisbaut, F. (2012). Control design for quantized linear systems with saturations. *IEEE Transactions on Automatic Control*, 57, 1883–1889.

Tarbouriech, S., Prieur, C., and Gomes Da Silva Jr, J.M. (2006). Stability analysis and stabilization of systems presenting nested saturations. *IEEE Transactions on Automatic Control*, 51(8), 1364–1371.

Ushiyama, T., Mizushige, K., Wakabayashi, H., Nakatsu, T., Ishimura, K., Tsuboi, Y., Maeta, H., and Suzuki, Y. (2008). Analysis of heart rate variability as an index of noncardiac surgical stress. *Heart and Vessels*, 23, 53–59.

van Heusden, K., West, N., Umedaly, A., Ansermino, J., Merchant, R., and Dumont, G. (2014). Safety, constraints and anti-windup in closed-loop anesthesia. In *World IFAC Congress*, 5496–5501. Cape Town, South Africa.

Zabi, S., Queinnec, I., Tarbouriech, S., Garcia, G., and Mazerolles, M. (2015). New approach for the control of anesthesia based on dynamics decoupling. In *9th IFAC Symposium on Biological and Medical Systems (BMS 2015)*. Berlin, Germany.

Zabi, S., Queinnec, I., Tarbouriech, S., and Mazerolles, M. (2016). Dynamic output-feedback controller design for analgesia guided by the pupil size variation. In *European Control Conference (ECC 2016)*. Aalborg, Denmark.

Zaccarian, L. and Teel, A. (2011). *Modern Anti-windup Synthesis: Control Augmentation for Actuator Saturation: Control Augmentation for Actuator Saturation*. Princeton Series in Applied Mathematics. Princeton University Press.

Zhusubaliyev, Z., Medvedev, A., and Silva, M. (2014). Nonlinear dynamics in closed-loop anesthesia: Pharmacokinetic/pharmacodynamic model under pid-feedback. In *American Control Conference*, 5496–5501. Portland, USA.

8. ANNEX

Proof of Proposition 1 : One has to prove that the trajectories of the closed-loop system (9) initialized in $\mathcal{E}(P,\eta)\setminus\mathcal{E}(P)$ converge to $\mathcal{E}(P)$.

Consider, for the closed-loop system (8), the quadratic Lyapunov function $V(x) = x'Px$, $P = P' > 0$. One has then to prove that $\dot{V}(x) < -\alpha(V(x))$, α being a $\mathcal{K}$-function, for any x such that $x'Px \leq \eta^{-1}$ and $x'Px \geq 1$. In other words, we have to verify by using the S-procedure the following inequality:

$$\dot{V}(x) + \tau_1(x'Px - 1) + \tau_2(\eta^{-1} - x'Px) < -\alpha(V(x)) \quad (30)$$

Furthermore, by using Lemmas 1 and 2, a sufficient condition to verify (30) is that

$$\begin{aligned}&\dot{V}(x) + \tau_1 x'Px - \tau_2 x'Px - \psi' S_1 \psi \\ &-2\psi' S_1(\psi + Cx) - 2\phi' T(\phi + D_c\psi + Gx) < -\alpha(V(x))\end{aligned} \quad (31)$$

and

$$trace(S_1)\Delta^2 - \tau_1 + \tau_2\eta^{-1} < 0 \quad (32)$$

as long as $\mathcal{E}(P,\eta) \subseteq S(u_0)$, which is ensured by satisfying inequality (15). The inequality (31) can be written as $\zeta'\mathcal{L}\zeta < -\alpha(V(x))$, with $\zeta = [x'\ \psi'\ \phi']'$ and $\mathcal{L}$ is the left-hand side matrix of inequality (14). Hence, the satisfaction of inequalities (14) and (16) means that it exists a small enough positive scalar α such that $\dot{V}(x) + \tau_1(x'Px - 1) - \tau_2(x'Px - \eta^{-1}) \leq -\alpha x'x$, which in turns gives (30). Moreover, one has to prove that the set $\mathcal{A}_0 = \mathcal{E}(P,\eta)$ contains the set $\mathcal{A}_\infty = \mathcal{E}(P)$ which holds if $\eta \leq 1$. ■

Proof of Proposition 2: Considering the matrix P defined in (24), one can define

$$\mathbb{J} = \begin{bmatrix} Y & V \\ I & 0 \end{bmatrix} \quad (33)$$

which is a nonsingular matrix as U and V are assumed to be nonsingular. Then, by pre- and post-multiplying condition (14) by $diag\{\mathbb{J}, I, S, I\}$ and $diag\{\mathbb{J}', I, S, I\}$, with $S = T^{-1}$, one gets

$$\begin{bmatrix} He(\mathbb{J}PA\mathbb{J}') + (\tau_1 - \tau_2)\mathbb{J}P\mathbb{J}' & \star & \star \\ B_\psi{}'P\mathbb{J}' - S_2C\mathbb{J}' & -S_1 - 2S_2 & \star \\ SB_\phi{}'P\mathbb{J}' - G\mathbb{J}' & -D_c & -2S \end{bmatrix}$$

Let us consider the following changes of variables

$$\begin{bmatrix} W & L \\ M & N \end{bmatrix} = \begin{bmatrix} XA_pY & 0 \\ \star & 0 \end{bmatrix} +$$

$$\begin{bmatrix} U & XB_p \\ 0 & I \end{bmatrix} \begin{bmatrix} A_c & B_c \\ C_c & D_c \end{bmatrix} \begin{bmatrix} V' & 0 \\ C_pY & I \end{bmatrix},$$

$$Z_1 = G_1,\ Z = G_1Y + G_2V',\ R = XB_pS + UE_cS.$$

with $G = [G_1\ G_2]$. It turns out, after calculations, that $\mathbb{J}PA\mathbb{J}' = H_1$, $\mathbb{J}P\mathbb{J}' = H_2$, $\mathbb{J}PB_\psi - \mathbb{J}C'S_2 = H_3$ and $\mathbb{J}PB_\phi - \mathbb{J}K' = H_4$. Then, one obtains relation (21). Relation (22) is obtained by pre- and post-multiplying (15) $diag\{\mathbb{J}, I\}$ and $diag\{\mathbb{J}', I\}$ and by noting $\mathbb{J}(K'_{(i)} - G'_{(i)}) = H_5$. ■