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Abstract: Set theory and invariant sets are the key ingredients used in this paper to address the control problem of general anesthesia. The paper is dedicated to adapt such tools in order to validate the multi-phase control law used in practice from the induction phase corresponding to the administration of an open-loop bolus dose to the maintenance phase of the depth of hypnosis during the surgical operation.

Keywords: Anesthesia, biomedical systems, constrained control, computational methods.

1. INTRODUCTION

General anesthesia plays an important role to provide surgeons adequate conditions for operation and avoid discomfort or pain for the patient while reducing the negative post-operation effects of anesthesia. In medical practice, anesthesia typically considers the administering of hypnotic and analgesic drugs monitored by the anesthetist by examining reliable indicators, as in particular the bispectral index (BIS). Although dosing guidelines are provided taking into account the inter-patient pharmacokinetic and pharmacodynamic variability, automated closed-loop control (in particular of Propofol addition) using the BIS has shown to be of great help not only to increase the control efficiency and but also to preserve the vigilance of anesthetists for potential critical events (Dumont (2012), Hemmerling (2009)). Several approaches have been proposed in the literature, from simple PI control to more complex adaptive control strategies (Bailey and Haddad (2005), Lemos et al. (2014), Beck (2015), Zabi et al. (2015), Ionescu et al. (2008)) and some of them have been validated in clinical experiments (van Heusden et al. (2014), Absalom and Kenny (2003)).

Such closed-loop control strategies apply from the initial induction phase (Nascu et al. (2015), Caruso et al. (2009)) but, generally, do not mimic the medical practice involving the administering of an initial bolus dose of drug prior to switching to the closed-loop control phase. Then, the original contribution of the paper pertains to mathematically validate the medical strategy, which reveals to be a multi-phase control law fitting the complete process from the induction phase corresponding to the administering of an open-loop bolus dose to the maintenance phase of the depth of hypnosis during the surgical operation. The control methods that we are going to design are based on set theory and in particular on invariant sets (see, for example, Blanchini and Miani (2008)), which allow ensuring that the evolution of a system can be indefinitely maintained within a given set of the state space. Actually, tools provided by invariance are particularly suited to manage the constraints, which result from the objective to maintain a given depth of hypnosis (constraint on the state or the output of the system) and to take into account the limitations of drug addition.

The paper is organized as follows. In Section 2, the pharmacokinetic and pharmacodynamic model of hypnosis by Propofol intravenous addition, together with the problem we intend to solve, are presented. The maintenance phase control design is addressed in Section 3.2, which guarantees that the depth of hypnosis is confined in an invariant set during the surgical operation phase. The induction phase control is then studied in Section 3.3 to steer the system trajectories toward the maintenance invariant set. Finally, the overall control scheme is summarized in Section 3.4. Numerical application of the control scheme is provided in Section 4. Concluding remarks end the paper in Section 5.

Notation. The notation throughout the paper is standard. The scalars A_{ij}, $i = 1,\dots,I$, $j = 1,\dots,J$, denote the elements of matrix $A \in \mathbb{R}^{I\times J}$. Similarly, the scalars B_i, $i = 1,\dots,I$, denote the elements of the vector $B \in \mathbb{R}^I$. $A_{(i)}$ denotes the i^{th} row of matrix A. For two sets S_1 and S_2, $S_1 \backslash S_2$ denotes the set S_1 deprived of S_2.

2. DYNAMICAL MODEL OF THE HYPNOSIS DYNAMICS

2.1 Continuous-time model

The dynamical model used to describe the drug effect during the patient hypnosis by Propofol intravenous addition is a standard pharmacokinetic/pharmacodynamic model (Minto et al. (1997), Schnider et al. (1998), Bailey and Haddad (2005)). It is based on the three-compartment model expressing the evolution of the drug concentrations in the blood (x_b), in the muscles (x_m) and in the fat (x_f) of the anesthetized patient, associated with the evolution of the effect-site compartment (the brain) concentration, denoted by the variable C_{eff}, considered as a quantifier of the Propofol effect on the patient depth of hypnosis. The

dynamics of C_{eff} is modeled as a first order system with the Propofol concentration in the blood as the input, that is

$$\dot{C}_{eff} = -k_1 C_{eff} + k_2 x_b,$$

with k_1 and k_2 positive scalars. Thus, provided that the drug concentration in the blood is stable at $x_{b,e}$, the value of C_{eff} converges exponentially to $x_{b,e}k_2/k_1$. Then the overall anesthesia dynamics is given, in continuous-time, by:

$$\dot{x} = A_c x + B_c u \tag{1}$$

with

$$A_c = \begin{bmatrix} -k_1 & k_2 & 0 & 0 \\ 0 & -a_{bm} - a_{bf} - d_b & a_{mb} & a_{fb} \\ 0 & a_{bm} & -a_{mb} & 0 \\ 0 & a_{bf} & 0 & -a_{fb} \end{bmatrix}, \; B_c = \begin{bmatrix} 0 \\ b \\ 0 \\ 0 \end{bmatrix} \tag{2}$$

and $x = [\, C_{eff} \;\; x_b \;\; x_m \;\; x_f \,]^T \in \mathbb{R}^4$ and $u \in [0, u_M]$ is the drug diffusion rate in mg/min. The numerical values determining the system dynamics are taken from the literature on anesthesia, see Schnider et al. (1998), Bailey and Haddad (2005):

$$d_b = \frac{Cl_1}{V_1}, \quad a_{bm} = \frac{Cl_2}{V_1}, \quad a_{bf} = \frac{Cl_3}{V_1}, \quad b = 1$$
$$a_{mb} = \frac{Cl_2}{V_2}, \quad a_{fb} = \frac{Cl_3}{V_3}, \quad k_1 = 0.456, \quad k_2 = \frac{k_1}{V_1}$$

where

$V_1 = 4.27, \;\; V_2 = 18.9 - 0.391(\text{age} - 53), \;\; V_3 = 238,$
$Cl_1 = 1.89 + 0.0456(\text{weight} - 77) - 0.0681(\text{LBM} - 59)$
$\quad +0.0264(\text{height} - 177),$
$Cl_2 = 1.29 - 0.024(\text{age} - 53),$
$Cl_3 = 0.836,$

with lean body mass (LBM)

- for male: $\text{LBM} = 1.1\text{weight} - 128\dfrac{\text{weight}^2}{\text{height}^2}$,
- for female: $\text{LBM} = 1.07\text{weight} - 148\dfrac{\text{weight}^2}{\text{height}^2}$.

It has to be noticed that, as experimental tests prove, the dynamics of C_{eff} and x_b are much faster than those concerning x_m and x_f. The control objective is to steer the value of C_{eff} to an optimal value, related to the desired patient sleep depth, or at least to close values, as fast as possible and then to maintain such a value along the intervention.

The effect-site concentration is related to the value of the bispectral index BIS, which is an indicator of the degree of sleep of the patient, through a nonlinear function (Bailey and Haddad (2005)). The BIS value takes values between 0 and 100, with 100 denoting full wakefulness, and it is a nonlinear function of C_{eff}. It is in practice a sigmoidal function of the effect-site C_{eff} given by

$$\text{BIS}(C_{eff}) = \text{BIS}_0 \left(1 - \frac{C_{eff}^{\gamma}}{C_{eff}^{\gamma} + \text{EC}_{50}^{\gamma}} \right) \tag{3}$$

with $\text{EC}_{50} = 5.6\,\mu$g/ml concentration at half maximal effect and $\gamma = 2.39$ (Bailey and Haddad (2005)).

2.2 Equilibria

The desired equilibrium is the one such that BIS $= 50$ and with associated $C_{eff}(50) = \text{EC}_{50}$ solution to equation (3). The value of the drug concentration in the blood that maintains the desired value of EC_{50} is then

$$x_{b,e} = \frac{k_1}{k_2}\text{EC}_{50},$$

and at the equilibrium, one has the unique solution to

$$\begin{bmatrix} u_e \\ x_{m,e} \\ x_{f,e} \end{bmatrix} = -\begin{bmatrix} b & a_{mb} & a_{fb} \\ 0 & -a_{mb} & 0 \\ 0 & 0 & -a_{fb} \end{bmatrix}^{-1} \begin{bmatrix} -a_b \\ a_{bm} \\ a_{bf} \end{bmatrix} x_{b,e} \tag{4}$$

allowing to define $x_e = \begin{bmatrix} \text{EC}_{50} & x_{b,e} & x_{m,e} & x_{f,e} \end{bmatrix}^T$ and u_e.

2.3 Discrete-time model

The control approach based on set theory used in this paper manipulates discrete-time models. Then, in the following, we consider the discretized version of the overall dynamic model (1), denoted as follows:

$$x^+ = Ax + Bu = e^{A_c t_s} x + \int_0^{t_s} e^{A_c(t_s - \tau)} B_c \, d\tau \, u, \tag{5}$$

with sampling time t_s.

Remark 1. In the continuous-time model (1), the evolution of drug in the annex compartments (muscles and fat) does not directly act on the evolution of the drug in the effect-site compartment. This is not formally the case in the discrete-time model (5). Furthermore, one can verify numerically that the direct effect of x_3 and x_4 on x_1 is much smaller than that one of x_2, being A_{13} and A_{14} of the order of 10^{-5}.

The control objective can be summarized as follows.

Problem 1. Determine a control strategy to control the induction and maintenance phases of the depth of hypnosis during surgical operation. In other words, characterize a control law $u(x)$ for system (5) composed of two successive steps as: (i) induction phase, which corresponds to (i-1) a high constant value of drug addition and (i-2) a zero addition of drug; and (ii) a control loop for the maintenance phase.

Throughout the paper, the first step related to induction phase is denoted by u_i, whereas the second one related to the maintenance one is denoted by u_r.

3. CONTROL DESIGN

In order to simplify the presentation of the control design based on the use of set theory techniques, we start with the maintenance phase control design.

3.1 Preliminaries on invariant set

Denoting with $X \subseteq \mathbb{R}^n$ and $U \in \mathbb{R}^m$ the state and input constraint sets respectively, we recall here the standard definition of invariant sets for generic nonlinear systems.

Definition 1. (Blanchini and Miani (2008)). The compact convex set $\Omega \subseteq \mathbb{R}^n$ with $0 \in \text{int}(\Omega)$ is an invariant set for the system $x^+ = f(x)$ if $\Omega \subseteq X$ and $f(x) \in \Omega$, for all $x \in \Omega$. It is a control invariant set for the controlled system $x^+ = f(x,u)$ if $\Omega \subseteq X$ and for every $x \in \Omega$ there exists $u(x) \in U$ such that $f(x,u(x)) \in \Omega$.

Then, every trajectory starting in an invariant set Ω remains in it. If Ω is a control invariant set then there exists a closed-loop admissible control that makes Ω invariant. In particular, the maximal (control) invariant set in X is the set of all the initial conditions whose trajectories do not violate the constraints represented by X (and U), see Blanchini and Miani (2008).

3.2 Maintenance phase control design

The constraints on the state and on the input are defined by the sets

$$\begin{aligned} X &= \{x \in \mathbb{R}^4 :\ C_{eff}(60) \le x_1 \le C_{eff}(40)\}, \\ U &= \{u \in \mathbb{R} :\ u_m \le u \le u_M\}, \end{aligned} \tag{6}$$

with $u_m = 0$.

Linear feedback control and nominal invariant set

The first step of the control design consists in computing the maximal invariant set in the space (x_1, x_2) given a linear feedback control and neglecting the effect of the states x_3 and x_4 on x_2. The latter assumption is not very reasonable, since it would mean to neglect the perturbation induced by the fat and muscle on the blood drug concentration. On the other hand, the dynamics of x_3 and x_4 are much slower than those of x_1 and x_2. This fact will be used, in Section 3.2.2, to infer and compensate their perturbing effect. For the moment, then, we consider the error system

$$z^+ = A_z z + B_z v, \tag{7}$$

where $z = (x_1 - \mathrm{EC}_{50},\ x_2 - x_{b,e})$, i.e. it is the projection on the subspace (x_1, x_2) of the vector $x - x_e$; the input is $v = u - u_e$ and $A_z \in \mathbb{R}^{2\times 2}$ and $B_z \in \mathbb{R}^2$ are the blocks of A and B associated to the subsystem (x_1, x_2) of system (5). From (6), the constraints on z and v are

$$\begin{aligned} Z &= \{z \in \mathbb{R}^2 :\ C_{eff}(60) - C_{eff}(50) \le z_1, \\ &\qquad z_1 \le C_{eff}(40) - C_{eff}(50)\}, \\ V &= \{v \in \mathbb{R} :\ u_m - u_e \le v \le u_M - u_e\}. \end{aligned} \tag{8}$$

A local state feedback control law $v = K_z z$, $K_z \in \mathbb{R}^{1\times 2}$, can be computed for stabilizing the system (7). The maximal invariant set Ω_z contained in $Z \cap K_z V$ for the system (7) in closed loop with control $v = K_z z$ can then be computed. Then, Ω_z is exactly the set of initial states of the system $z^+ = (A_z + B_z K_z)z$ whose related trajectories stay in Ω_z without violating the input constraints $v = K_z z \in V$.

Remark 2. The states x_1 and x_2 are assumed to be measured to realize $v = K_z z$. If only x_1 is available, by means of a measure of the BIS, then either x_2 is reconstructed through an observer (being the system (7) observable) or a feedback of the state x_1 only has to be designed. Notice that, the matrix A_z being Schur-Cohn, a stabilizing local output feedback control can always be designed.

Then, by controlling system (5) with the feedback control

$$u_n(k) = K(x - x_e) + u_e = [K_z\ 0\ 0](x - x_e) + u_e, \tag{9}$$

with $K \in \mathbb{R}^{1\times 4}$, one assures that the state (x_1, x_2) remains in $\Omega = \Omega_z + (\mathrm{EC}_{50},\ x_{b,e})$ in absence of the perturbing effect of x_3 and x_4. Nevertheless, since such an effect is not negligible in general (at least during the first minutes, when the state values are far from the equilibrium), the property of invariance might be violated unless a perturbation compensation is applied.

Linear feedback with perturbation compensation

The next step consists in designing a simple compensation of the effect of x_3 and x_4 on x_1 and x_2, or equivalently, on z_1 and z_2. From the numerical values given below it can be noticed that A_{13} and A_{14} are much smaller than A_{23} and A_{24} and then the direct effect of x_3, x_4 on z_1 could be assumed negligible for the moment. Moreover the value of B_1 is much smaller than that one of B_2. Then, we just consider the effect of x_3 and x_4 on z_2 that is

$$d = d(x_3, x_4) = A_{23}(x_3 - x_{m,e}) + A_{24}(x_4 - x_{f,e}) \tag{10}$$

bounded in

$$D = \{d \in \mathbb{R} :\ -A_{23}x_{m,e} - A_{24}x_{f,e} \le d \le 0\}.$$

The bound $d \le 0$ comes from the implicit assumption that the drug concentrations in the muscles and in the fat are never higher than the equilibrium concentration. This assumption, reasonable in general, is always satisfied during a large initial time interval, since x_3 and x_4 start at 0 and slowly increase, due to their dynamics, during a long a time interval.

By defining $w_3 = x_3 - x_{m,e}$ and $w_4 = x_4 - x_{f,e}$, from (10) it follows that

$$d(k) = A_{23}w_3(k) + A_{24}w_4(k), \tag{11}$$

Therefore, by applying to system (5) the control

$$u_c(k) = [K_z\ 0\ 0](x(k) - x_e) + u_e - \frac{d(k)}{B_2}, \tag{12}$$

from (7) we can compute the dynamics of z_1 and z_2 as follows:

$$\begin{aligned} z_1(k+1) &= C_{eff}(k+1) - \mathrm{EC}_{50} \\ &= A_{11}C_{eff}(k) + A_{12}x_2(k) + A_{13}x_3(k) + A_{14}x_4(k) \\ &\qquad + B_1K_z z(k) + B_1u_e - \frac{B_1}{B_2}d(k) - \mathrm{EC}_{50} \\ &= \left(A_z + B_zK_z\right)_{(1)} z(k) \\ &\quad + (A_{13} - \frac{B_1}{B_2}A_{23})w_3(k) + (A_{14} - \frac{B_1}{B_2}A_{24})w_4(k). \end{aligned} \tag{13}$$

and

$$\begin{aligned} z_2(k+1) &= x_2(k+1) - x_{b,e} \\ &= A_{22}x_2(k) + A_{23}x_3(k) + A_{24}x_4(k) \\ &\qquad + B_2K_z z(k) + B_2u_e - d(k) - x_{b,e} \\ &= A_{22}z_2(k) + B_2K_z z(k) \\ &= \left(A_z + B_zK_z\right)_{(2)} z(k), \end{aligned} \tag{14}$$

where the third equality holds from the equilibrium condition (4).

At this step, we consider the following two assumptions:

Assumption 1. The terms $(A_{13} - \frac{B_1}{B_2}A_{23})w_3(k)$ and $(A_{14} - \frac{B_1}{B_2}A_{24})w_4(k)$ in (13), related to the effects of x_3 and x_4 on z_1, are negligible.

Assumption 1 is reasonable since $A_{13} - \frac{B_1}{B_2}A_{23}$ and $A_{14} - \frac{B_1}{B_2}A_{24}$ are related to direct effect of x_3 and x_4 on x_1, which is null in the continuous-time model (1)-(2).

Assumption 2. $x_3(k) < x_{m,e}$ and $x_4(k) < x_{f,e}$ for all $k \in \mathbb{N}$.

Assumption 2 can be supposed to hold during the whole anesthesia period, in practice. In fact, the objective of the control being to steer the whole state at x_e, the states x_1 and x_2, whose dynamics are much more rapid than those of x_3 and x_4, would be driven relatively fast around the equilibrium values of EC_{50} and $x_{b,e}$, by every reasonable control strategy. The drug, then would diffuse slowly in the muscles and the fat, until they also reach the equilibrium. However, due to their slow dynamics, the increasing of x_3 and x_4 would last for a long period before their values could be close to $x_{m,e}$ and $x_{f,e}$.

Suppose that u_M is large enough and the control smooth enough to avoid excessive excitation of the control action due to surgi-

cal perturbations (as intubation, incision). Then, the following proposition can be stated.

Proposition 1. Suppose that Assumptions 1 and 2 hold. The system (5) in closed loop with control (12) is exponentially stable and does not violate the constraints $x \in X$ and $u \geq 0$ if the initial state belongs to Ω.

Proof. Since the set Ω_z is an invariant set for the system $z^+ = (A_z + B_z K_z)z$, thus, from Assumption 1, if $z(0) \in \Omega_z$ then $z(k) \in \Omega_z$ and $K_z z(k) \in V$ for all $k \in \mathbb{N}$. This implies, first, that $x(k) \in \Omega$ for all $k \in \mathbb{N}$ if $x(0) \in \Omega$. Moreover, since $K_z z(k) \in V$, then $K_z z(k) \geq u_m - u_e = -u_e$ and equivalently $[K_z \; 0 \; 0](x(k) - x_e) + u_e \geq 0$. Since $d(k) < 0$ for all $k \in \mathbb{N}$, from Assumption 2, then $u_c(k) > [K_z \; 0 \; 0](x(k) - x_e) + u_e \geq 0$ for $k \in \mathbb{N}$. □

The main problem with the corrected control u_c defined in (12) is that it is a feedback of the current values of the drug concentrations in the muscles and in the fat that are not available. One solution could be the design of an observer to reconstruct their value on-line. Nevertheless, due to the fact that the dynamics of x_3 and x_4 are consistently slower than those of x_1 and x_2, then the value of $d(k)$, as defined in (11), can be reasonably considered to be constant between two sampling instants. From (11), by manipulating the dynamics of x_2, one can write:

$$\begin{aligned} d(k-1) \; &= x_2(k) - A_{22}x_2(k-1) - B_2 u(k-1) \\ &\quad - A_{23}x_{m,e} - A_{24}x_{f,e}. \end{aligned} \tag{15}$$

Thus, the control law to be applied during the maintenance phase results in

$$u_r(k) = [K_z \; 0 \; 0](x(k) - x_e) + u_e - \frac{d(k-1)}{B_2}, \tag{16}$$

where $d(k-1)$ is defined in (15) with $u(k-1) = u_r(k-1)$. The linear control u_r defined in (16) is such that, in practice, the set Ω is invariant for system (5) and then, once attained, the state does not leave Ω, despite the perturbation. This implies clearly the constraints satisfaction, i.e. the BIS is maintained between 40 and 60. Moreover the state converges to the equilibrium point x_e and then the BIS to 50. The drawback of this control law is that it is effective once the state is inside Ω, while there is not assurance that its application is efficient outside Ω. One possibility to deal with this problem is to design a simple control law to be applied outside Ω that drives the state in Ω.

3.3 Induction phase control

One of the objective is to induce the hypnosis as fast as possible, that means to steer the state within the band BIS $\in [40,\ 60]$. Then, the first part of the control, related to the induction phase, is assumed to be a constant control, with u as high as possible but such that the BIS never reaches values lower than 40.

For this aim we compute the maximal control invariant, denoted Ω_c, for the nominal system (7) contained in the band on $z_1 \in [C_{eff}(60) - \mathrm{EC}_{50},\ C_{eff}(40) - \mathrm{EC}_{50}]$ corresponding to the band on BIS $\in [40,\ 60]$. These points, in fact, are those that can be stirred towards the equilibrium x_e by means of an appropriate control input, nonlinear in general, without violating the constraints. Note that the maximal control invariant set Ω_c is always greater or equal than the invariant set related to any control law.

Let us neglect once more the perturbation due to x_3 and x_4, for the moment, and recall that the aim of the first part of the induction phase control is to steer as fast as possible x_1 in the band $[C_{eff}(60),\ C_{eff}(40)]$ assuring that no constraint violation eventually occurs. Then, the first part of the induction phase control should be the higher constant value of u, which we denote by u_0, such that the trajectory reaches $\Omega_0 = \Omega_c + (\mathrm{EC}_{50},\ x_{b,e})$. By construction, a state is in the control invariant if and only if it can be maintained indefinitely by an appropriate admissible control. The value of u_0 can be obtained from the shape of Ω_0, solving

$$\begin{aligned} (u_0, T_0) = \arg\min_{u,T} \; & T \\ \text{s.t. } & [1\;0\;0\;0] \cdot \int_0^T e^{A_c(T-\tau)} B_c d\tau \cdot u = C_{eff}(60), \\ & [0\;1\;0\;0] \cdot \int_0^T e^{A_c(T-\tau)} B_c d\tau \cdot u = x_2^M, \end{aligned} \tag{17}$$

with $x_2^M = \max\{x_2 : (x_1, x_2) \in \Omega_0\}$.

Now, what is left to design is a simple control law to be applied once the state is in Ω_0 to steer it in Ω, where the control u_r can be applied efficiently. To do that, consider Figure 1, that shows the successors of the vertices of Ω_c, by using the data provided in Section 4. Indeed for every vertex p, in red is represented the segment that joins the vertex with $A_z p$, and in black the points $A_z p + V$, with V as in (8), that is the set of all the states in the space z reachable in one step from p. As a test for the control invariance, notice that every vertex can reach the set Ω_c through an extremal control action. Moreover, and more interestingly, notice that for states with high value of z_2, the input to be applied is the smaller one, i.e. $v = -u_e$ and equivalently $u = u_m = 0$, while for states with negative values of z_2, a large value of u close to u_M has to be applied. This is reasonable, since if one wants x_2 to decrease, then the drug deliverance should be stopped, while to increase it the most, u_M should be applied. Therefore, the input to apply for x_1 in the band $[C_{eff}(60),\ C_{eff}(40)]$ when x_2 is above the set Ω is $u = 0$, while it is $u = u_M$ if x_2 is below Ω.

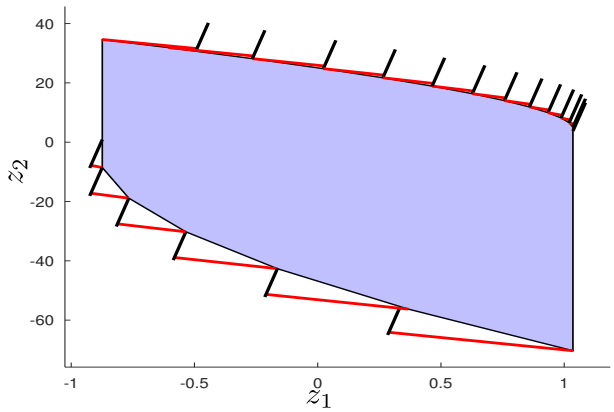

Fig. 1. Maximal control invariant set Ω_c in Z and vertices successors.

Summarizing, the following induction phase control has to be applied to make the states (x_1, x_2) reach Ω rapidly avoiding constraints violations:

$$u_i(x) = \begin{cases} u_o, & \text{if} \quad x_1 < C_{eff}(60), \\ 0, & \text{if} \quad x_2 > x_{b,e},\ (x_1, x_2) \in \Omega_0 \backslash \Omega, \\ u_M, & \text{if} \quad x_2 < x_{b,e},\ (x_1, x_2) \in \Omega_0 \backslash \Omega, \end{cases} \tag{18}$$

recalling that $\Omega = \Omega_z + (\mathrm{EC}_{50},\ x_{b,e})$ and $\Omega_0 = \Omega_c + (\mathrm{EC}_{50},\ x_{b,e})$, where Ω_z and Ω_c are the maximal invariant and control invari-

ant sets in the band $x_1 \in [C_{eff}(60),\ C_{eff}(40)]$ for the system (7). These sets are depicted in Figure 2.

Finally, we consider the effect of the disturbance due to x_3 and x_4 in the induction phase. Such a disturbance has a beneficial effect when x_1 is in the band $[C_{eff}(60),\ C_{eff}(40)]$ and $x_2 > x_{b,e}$, which is equivalent to $z \in Z$ and $z_2 > 0$. In fact, since in practice $x_3 < x_{m,e}$ and $x_4 < x_{f,e}$, i.e. $w_3 < 0$ and $w_4 < 0$, then d is always negative. In particular d starts from its minimum, $-A_{23}x_{m,e} - A_{24}x_{f,e}$, and increases converging to 0, thus d is very small during the first minutes. Therefore, after the first part of the induction phase, if the value of x_2 is high, the effect of d combines with u_i in (18) to drive the state (x_1, x_2) in Ω. On the other side, i.e. if $z \in Z$ and $z_2 < 0$, the effect of d is opposite to u_i, but the higher margin on the control (u_M is the active bound at low values of x_2) can easily compensate d. This is because low values of the drug in the blood can be increased quickly by the drug injection.

3.4 Overall control scheme

By combining the induction phase control u_i defined in (18) and the maintenance control law u_r defined in (16), a solution to Problem 1 can be stated. Indeed, the multi-phase control law, which mimics the medical practice can be defined as follows:

$$u(x) = \begin{cases} u_i(x), & \text{if } (x_1, x_2) \notin \Omega, \\ u_r(x), & \text{if } (x_1, x_2) \in \Omega, \end{cases} \tag{19}$$

with $\Omega = \Omega_z + (\mathrm{EC}_{50},\ x_{b,e})$.

4. APPLICATION

The application of the control law (19) has been simulated for a given patient (female) of 46 years-old, 54 kg and 163 cm. The discretized system (5) obtained with a sampling time of 6 seconds is given by the following data:

$$A = \begin{bmatrix} 0.9554 & 0.0100 & 0.0000 & 0.0000 \\ 0 & 0.9117 & 0.0064 & 0.0003 \\ 0 & 0.0325 & 0.9934 & 0.0000 \\ 0 & 0.0187 & 0.0001 & 0.9997 \end{bmatrix}, \tag{20}$$

$$B = [\,0.0005,\ 0.0955,\ 0.0017,\ 0.0009\,]^T.$$

The equilibrium corresponding to a target BIS of 50 is then given by:

$$u_e = 9.3008[\mathrm{mg/min}], \quad x_{b,e} = 23.912[\mathrm{mg}],$$
$$x_{m,e} = 121.167[\mathrm{mg}], \quad x_{f,e} = 1332.8[\mathrm{mg}].$$

The constraints on the state and the bounds on the input are given by the sets

$$X = \{x \in \mathbb{R}^4 :\ 4.7262 \le x_1 \le 6.6354\}, \tag{21}$$
$$U = \{u \in \mathbb{R} :\ 0 \le u \le 100\},$$

The constraints on z and v are

$$Z = \{z \in \mathbb{R}^2 :\ -0.8738 \le z_1 \le 1.0354\}, \tag{22}$$
$$V = \{v \in \mathbb{R} :\ -9.3008 \le v \le 90.6992\},$$

and the effect of x_3 and x_4 on z_2 is bounded in

$$D = \{d \in \mathbb{R} :\ -1.2243 \le d \le 0\}.$$

Then, one can check that the terms $A_{13} - \dfrac{B_1}{B_2}A_{23}$ and $A_{14} - \dfrac{B_1}{B_2}A_{24}$, are small:

$$A_{13} - \frac{B_1}{B_2}A_{23} = 3.9357 \cdot 10^{-8}, \tag{23}$$
$$A_{14} - \frac{B_1}{B_2}A_{24} = 1.0729 \cdot 10^{-10},$$

which validate Assumption 1.

The local state feedback control gain $K_z \in \mathbb{R}^{1\times 2}$ is a LQR control computed with parameters $Q = \mathrm{diag}[15,\ 1]$ and $R = 1.8$. These parameters have been selected after a series of choices to improve the size of the related invariant set.

The overall control u (19) is compared with the control laws u_n and u_r, as defined in (9) and (12) applied as soon as $x \in X$. In Figure 2, the trajectory generated by the control law (19) is depicted in black. It can be seen that, after the first part of the induction phase, the state enters the band X (but not in Ω), and then the control is switched off, to make the trajectory drop toward Ω. Once in Ω, the control u_r is applied that makes Ω invariant, thus preventing any constraints violation, and steers the state at x_e. In blue, the trajectory obtained by using u_c (that is an improved version of u_n) when x enters X, is plotted. Notice that this control law, tailored for the states in Ω is not able to prevent the violation of $x_2 \le 6.6354$ and has good behavior only once $x \in \Omega$. In red, it is drawn the trajectory obtained by applying u_n after entering X. Notice that the presence of the disturbance has beneficial effects in the first instants, indeed, the state drops quickly in the safe region Ω. Nevertheless, not being Ω invariant in presence of perturbation, the trajectory leaves eventually the set and does not converge to the desired x_e until the perturbation effect is disappeared.

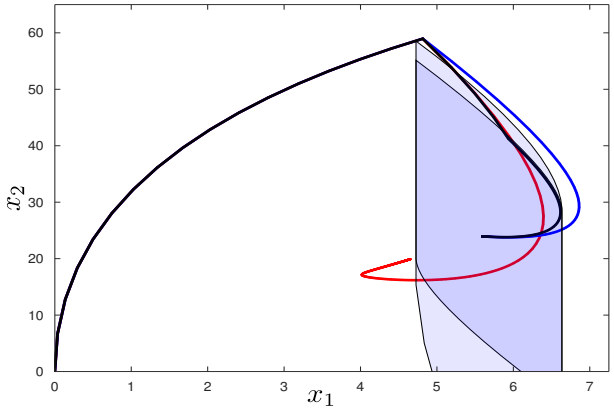

Fig. 2. Comparison between u as (19), in black, u_n as in (9) applied when $x \in X$, in red, and u_r as in (16) applied when $x \in X$, in blue. The invariant set Ω is in mild blue and the control invariant set Ω_c in light blue.

It is finally worth remarking that, since, as noticed above, the disturbance has beneficial effect during the first instants, the black trajectory reaches Ω although the state is not initially in Ω_0 once in X. This has an important implication: the perturbation effect during the critical instants just after the first part of the induction phase can be neglected with no risk. The control invariant set is still invariant and bigger regions of the state could be aimed at to reach Ω. Thus, the control invariant set is only a bit conservative, there is not risk of constraint violation if considered as first aim of the induction phase.

Figure 3 represents the evolution of the value of the variable BIS and the value of the blood concentration along the trajectory generated by the control law u defined in (19). Then, the BIS is stirred to the desired value of 50 while avoiding the constraints violations. Also the moment of the switch between 0 and u_r can be remarked along the trajectory in the band $40-60$.

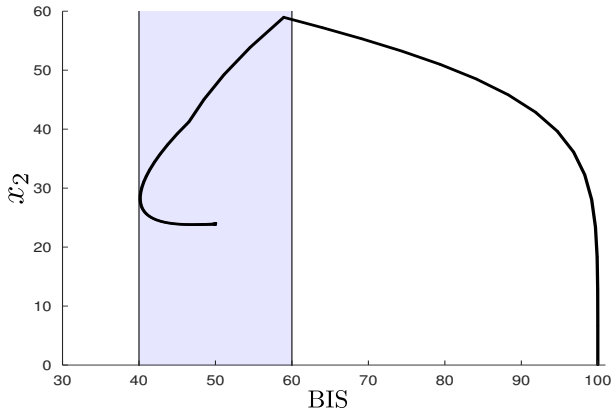

Fig. 3. BIS and x_2 state-space evolution generated with u as (19).

Finally, Figure 4 illustrates the closed-loop time evolution of the state and input u generated with (19). It illustrates both the efficiency of the proposed control strategy and the slow evolution of the state x_3 and x_4, which will attain their equilibrium value after a long time.

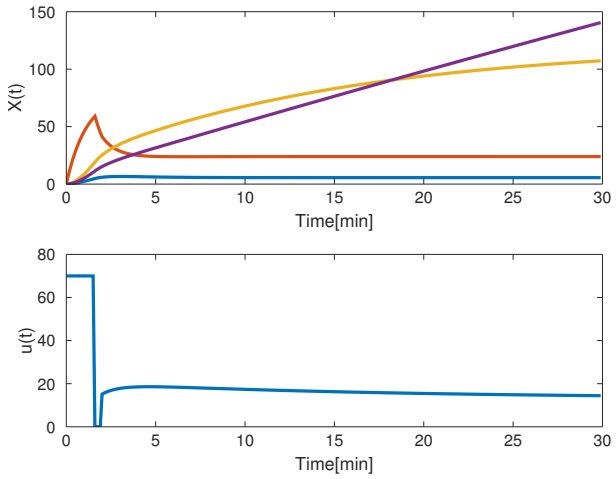

Fig. 4. Time-evolution of the hypnosis induction and maintenance. Top: State evolution in closed-loop. x_1 in blue; x_2 in red; x_3 in yellow and x_4 in purple − Bottom: the input.

5. CONCLUSION

A control strategy based on set theory and invariant sets has been proposed to control the induction and maintenance phases of the depth of hypnosis during surgical operation. The control is formed of a succession of two main steps. First a high constant value of drug addition is used, followed by a zero addition of drug, and second, the control loop is closed when accessing the maintenance phase. The instants of switch between the phases are related to the trajectory entering in the maximal control invariant set and the maximal invariant set. The proposed control strategy results to mimic the heuristic induction and maintenance phase control commonly adopted by anesthetists.

The extension to parametric uncertain models, to deal with the inter- and intra-patient variability, is one objective of our ongoing research. Moreover, the fact to take into account the surgical perturbation (intubation, incision) and a certain level of performance thanks to the multi-phase control law proposed is also an interesting direction for future work.

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