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Abstract: This paper deals with the control of the induction phase of anesthesia. The objective during this first phase is to bring the patient from its awake state to a final state corresponding to some given depth of anesthesia, measured by the BIS (Bispectral index), within a minimum time. This optimal time control strategy is addressed by means of the maximum principle of Pontryagin. Furthermore, since the anesthesia model presents multiple time scale dynamics that can be split in two groups : fast and slow and since the BIS is a direct function of the fast ones, we only consider the optimal control of fast states. The final state of the slow dynamics is let free. The synthesis approach of the optimal control is detailed then tested in the case of a nominal patient.

Keywords: Anesthesia, Induction, Optimal control, Pontryagin principle.

1. INTRODUCTION

General anesthesia consists in the control of the perfusion of hypnotic and analgesic drugs based on clinical indicators such as heart rate, blood pressure and BIS (Bispectral index, derived from the spectral analysis of the electroencephalogram signal (EEG)). Automatic control techniques are used to increase patient comfort during surgery and recovery (Struys et al. (2001)), reduce dosing differences between doctors and decrease the workload of the anesthesiologists in order to minimize human error risk (Mackey (2012)).

A general anesthesia procedure may be divided into three temporal phases: induction, maintenance and reanimation. Indeed, in a traditional anesthesia approach, the anaesthesiologist starts by an initial injection of a big amount of drugs (bolus) for a short time (induction phase), followed by a phase of manual control corresponding to the maintenance phase. The stop of the administration of anesthetic drugs marks the transition from maintenance to the reanimation phase which ends with the full resumption of consciousness and physiological functions.

Most of the works tackling the automatic control of anesthesia suggest a single control law for the two phases (induction and maintenance) using different techniques such as PID-based feedback control (Absalom and Kenny (2003), Soltész (2013)), adaptive control (Haddad et al. (2003)) or other techniques as in Nascu et al. (2015). The disadvantage of such approaches can be seen in the overshoot of the BIS and in the abrupt variation of the flow rate that should be avoided for the actuator. On the other hand, there exists only few works that treat each phase apart as in Fiacchini et al. (2016) or propose a control of only the maintenance phase (Lemos et al. (2014)) or the induction phase (Cummings et al. (1984)). Moreover, studies generally focus on the control of one drug (hypnotic or analgesic) and we follow the same route considering only the hypnotic control of the patient.

In a precedent paper (Zabi et al. (2015)), we developed a new strategy for the robust control of anesthesia for the maintenance phase taking into account the saturation of the actuator, the multiple time scale dynamics in the anesthesia model and the variability of the patient. In the continuation of our work, this paper address the problem of control of the induction phase using the optimal control. This optimal control is chosen because it allows to better imitate the clinical practice (bolus injection to quickly converge towards the target). As in the maintenance phase, the multiple time scale in the dynamics is taken into account by considering that the target is only depending on the fast dynamics including the BIS. A simulation study performed on a nominal patient shows the pertinence of our approach.

2. MODELLING ASPECTS AND PROBLEM FORMULATION

2.1 The traditional patient model

The compartment model used to describe the circulation of drugs in a patient's body, also known as Pharmacokinetic/Pharmacodynamic (PK/PD) model, is based on a classical compartment model as shown in Figure 1 (Derendorf and Meibohm (1999)).

The effect of the drug on the patient is expressed throughout the effect site, which represents the action of drugs on

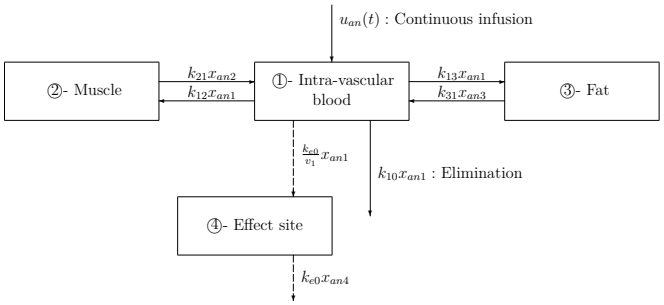

Fig. 1. The compartment model

the brain and is related to the concentration in the central compartment through a first order dynamic (Beck (2015)). So, the compartmental model can be expressed as follows:

$$\dot{x}_{an}(t) = Ax_{an}(t) + Bu_{an}(t) \tag{1}$$

with

$$A = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ k_{e0}/v_1 & 0 & 0 & -k_{e0} \end{bmatrix}$$

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

where $x_{an} = [x_{an1}\ x_{an2}\ x_{an3}\ x_{an4}]'$, $x_{an1}(t)$, $x_{an2}(t)$, $x_{an3}(t)$ are the masses in grams of the propofol in the different compartments and u_{an} is the infusion rate in g/min of the anesthetic.

The parameters $k_{ij} \geq 0,\ \forall i \neq j,\ i,j = 1,2,3$, are the transfer rates of the drug between compartments. The parameter k_{10} represents the rate of elimination from the central compartment. These parameters are functions of the patient characteristics (weight, age, height, ...) and the drug. There exists several empirical models, which give the relation between those parameters and patient's characteristics for a given drug (Coppens et al. (2011)). In particular one can cite the model of Schnider et al. (1998) (Table 1) that we use here to define a typical patient and predict the PK/PD model parameters when propofol is used as the hypnotic drug. The lean body mass (LBM) is calculated using the James formula (James (1976)) as follows:

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

The depth of anesthesia indicator widely used by clinicians is the BIS (the bispectral index). It is a signal derived from the EEG analysis, which quantifies the level of consciousness of a patient from 0 (no cerebral activity) to 100 (fully awake patient). It is commonly accepted that the BIS evolution is directly related to the effect site concentration of x_{an4}, and can be described empirically by a decreasing sigmoid function (Bailey and Haddad (2005)):

$$BIS(x_{an4}(t)) = BIS_0\left(1 - \frac{x_{an4}^{\gamma}(t)}{x_{an4}^{\gamma}(t) + EC_{50}^{\gamma}}\right), \tag{2}$$

BIS_0 is the BIS value of an awake patient typically set to 100. EC_{50} corresponds to drug concentration associated with 50% of the maximum effect and γ is a parameter modeling the degree of non-linearity. Typical values for these parameters are $EC_{50} = 3.4\mu g/ml$ and $\gamma = 3$ (Haddad et al. (2010)).

2.2 Equilibrium point

We consider generally that during a surgery, the BIS must be brought then maintained close to 50, or at least in an interval between 40 and 60. Given the sigmoid describing the relation between the BIS and the effect site concentration, it follows that for the BIS equal to 50% of BIS_0 the effect site concentration must be equal to EC_{50}. The values of the other variables can then be deduced from the unique equilibrium point of system (1) (see Zabi et al. (2015)).

$$x_{e1} = EC_{50}v_1,\ \ x_{e2} = \frac{k_{12}}{k_{21}}x_{e1},\ \ x_{e3} = \frac{a_{13}}{a_{31}}x_{e1},\ \ x_{e4} = EC_{50}$$

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

$$u_e = k_{10}x_{e1}$$

2.3 Error model

Considering the change of variables $x = x_{an} - x_e$ and $u = u_{an} - u_e$ with $x_e = [x_{e1}\ x_{e2}\ x_{e3}\ x_{e4}]'$, the error model can be described as:

$$\dot{x} = Ax + Bu \tag{3}$$

with $x = [x_1\ x_2\ x_3\ x_4]'$ and A defined in equation (1). The equilibrium point is, therefore, the origin of this error model. The amplitude of the control is constrained,

$$U_{min} \leq u(t) \leq U_{max} \tag{4}$$

where U_{min} is equal to $-u_e$ and $U_{max}+u_e$ is the maximum flow rate of the drug that can be administered in practice.

2.4 Problem formulation

Inspired by the clinical practice where, in order to quickly sedate the patient and bring his state near to the equilibrium x_e, the anaesthesiologist begins by a bolus injection, we propose the use of an optimal control strategy for the induction phase. This control strategy aims at bringing the patient state from its awake state $x_{an} = 0$ to the equilibrium target state $x_{an} = x_e$ (or equivalently bringing the error model state from an initial state $x = -x_e$ to the origin $x = 0$) in a minimum time.

Regardless of patient under consideration, the dynamics of metabolism and circulation of propofol in the central compartment and at the site effect is ten times faster than in muscles, and even a hundred times faster than in fat. The control of the fast dynamics is the most important because the regulation of the BIS is a direct function of the concentration at the effect site and thus of the fast dynamics on which the administered drug directly acts. Thus, in the following, we choose to separate the dynamics by denoting $x_f = [x_1\ x_4]$ the fast ones and $x_s = [x_2\ x_3]$ the slow ones.

Therefore, since the BIS is directly function of fast states, the fact of bringing the fast states to the origin allows a quick transfer of the BIS toward the target 50. Nevertheless, bringing the slow states to their origin will take a considerable time and has no direct effect on the BIS. Thus the strategy adopted, in this paper, consists at designing the optimal control law that brings the fast states to their origin in a minimum time regardless of the slow ones. Note

Table 1. Schnider Model

Parameter	Estimation	male, 53yr, 77kg, 177cm
$k_{10}(min^{-1})$	0.443 + 0.0107×(weight-77)-0.0159×(LBM-59)+0.0062×(height-177)	0.384
$k_{21}(min^{-1})$	0.302 - 0.0056×(age-53)	0.375
$k_{31}(min^{-1})$	0.196	0.196
$k_{12}(min^{-1})$	[1.29 - 0.024×(age-53)]/[18.9-0.391×(age-53)]	0.067
$k_{31}(min^{-1})$	0.0035	0.0035
$k_{e0}(min^{-1})$	0.456	0.456
$v_1(L)$	0.288× weight	22.176

that, afterwards, during the maintenance phase the slow ones may be considered as disturbances and the closed loop control objective will be to maintain the fast states near to the origin despite of the disturbances of the slow ones. The scheme in Figure 2 describes the approach of the induction phase followed by a maintenance phase.

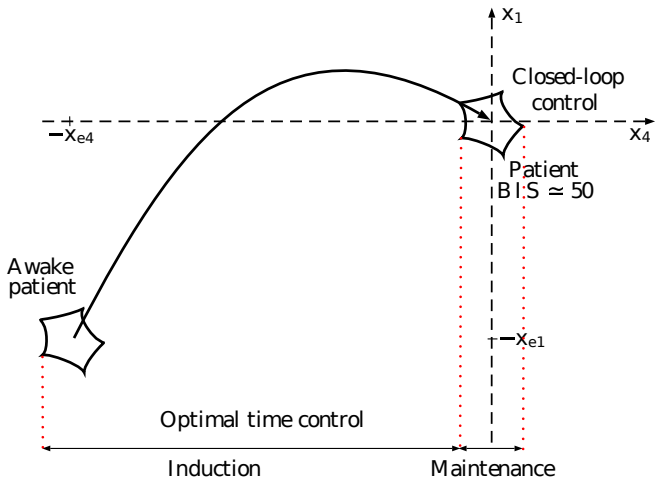

Fig. 2. Scheme describing the approach with an "induction phase" followed by the "maintenance phase"

The problem we intend to solve can be addressed as follows.

Problem 1. Let $x(0) = -x_e$ be the initial state of system (3), find the $u^*(t)$ satisfying the constraint (4) that allows bringing the fast states to the origin in a minimum time.

Formally, this minimum time control problem can then be written as follows

$$\begin{aligned} \min_{u(t)} \quad & J(x,u) = \int_0^{T_f} dt = T_f \\ \text{s. t} \quad & \dot{x}(t) = Ax + Bu, \;\; x(0) = -x_e, \; x_f(T_f) = 0 \\ & U_{min} \leq u(t) \leq U_{max} \end{aligned} \tag{5}$$

3. TIME-OPTIMAL CONTROL SYNTHESIS

The minimum time control problem has been studied extensively in the literature (see Liberzon (2012), Athans and Falb (1966)). In the case of linear systems, the existence and uniqueness of the solution is known to depend on the controllability of the system. Moreover, as we shall see later, this command consists of a countable number of commutations between U_{max} and U_{min}. Since the eigenvalues of the model are real, the number of switch is at most equal to $n-1$, where n is the order of the system, thus, at most three commutations in our case.

3.1 The Maximum principle

To solve the problem (5), we use the maximum principle of Pontryagin in the version given by Naidu (2002) recalled below, after the definition of the Hamiltonian:

Definition 1. The Hamiltonian H of problem (5) is written

$$H(t,x,u,\lambda) = 1 + \lambda'(Ax + Bu) \tag{6}$$

with $\lambda(t)$ a costate vector.

Theorem 1. (Maximum principle of Pontryagin). Let $u^*(t)$ be a control law that transfers the system (3) from the initial state $x(0) = -x_e$ to a final state where the fast states $x_f(T_f) = 0$ and let $x^*(t)$ be the trajectory corresponding to $u^*(t)$. In order that $u^*(t)$ be the minimum time control solution to problem (5), it is necessary that there exists a corresponding costate vector $\lambda^*(t)$ such that:

a. $\lambda^*(t)$ and $x^*(t)$ are solutions of the canonical equations:

$$\dot{x}^*(t) = \frac{\partial H}{\partial \lambda}(t, x^*, u^*, \lambda^*) \tag{7a}$$

$$\dot{\lambda}^*(t) = -\frac{\partial H}{\partial x}(t, x^*, u^*, \lambda^*) \tag{7b}$$

with the boundary conditions

$$x^*(0) = -x_e \qquad x_f^*(T_f) = 0. \tag{8}$$

b. $u^*(t)$ is a global minimum for the Hamiltonian in $[U_{min},\ U_{max}]$

$$\min_{u(t) \in [U_{min},\ U_{max}]} H(t, x^*, u, \lambda^*) = H(t, x^*, u^*, \lambda^*)$$

that is,

$$H(t, x^*, u, \lambda^*) \geq H(t, x^*, u^*, \lambda^*) \;\; \forall u \in [U_{min},\ U_{max}] \tag{9}$$

c. the Hamiltonian $H(t, x^*, u^*, \lambda^*)$ is equal to zero for all $t \in [0,\ T_f]$, i.e.,

$$H(t, x^*, u^*, \lambda^*) = 0 \; \forall t \in [0,\ T_f] \tag{10}$$

The conditions of Theorem 1 do not contain explicit informations regarding initial and final states of the costate vector, $\lambda^*(0)$ and $\lambda^*(T_f)$. Nevertheless, from the equation (10), we can verify that

$$\lambda^*(t) \neq 0 \qquad \forall t \in [0,\ T_f] \tag{11}$$

3.2 Characterization of the optimal solution

Using the maximum principle of Pontryagin, we can develop the solution of the minimum time problem (5) as

follows: first, the optimal trajectories of $x^*(t)$ and $\lambda^*(t)$ satisfy the canonical equations (7a) and (7b) then

$$\dot{x}^*(t) = Ax^*(t) + Bu^*(t) \tag{12a}$$
$$\dot{\lambda}^*(t) = -A'\lambda^*(t) \tag{12b}$$

with $x^*(0) = -x_e$, $x_f^*(T_f) = 0$ and $\lambda^*(0) \neq 0$.

Then, from the optimality condition (9), the control law $u^*(t)$ is a global minimum of the Hamiltonian if

$$1 + \lambda^{*'}(t)Ax^*(t) + \lambda^{*'}(t)Bu^*(t) \leq 1 + \lambda^{*'}(t)Ax^*(t) + \lambda^{*'}(t)Bu(t) \ \forall u \in [U_{min},\ U_{max}]$$

Or, equivalently, if

$$\lambda^{*'}(t)Bu^*(t) \leq \lambda^{*'}(t)Bu(t) \quad \forall u \in [U_{min},\ U_{max}]$$

If $\lambda^{*'}(t)B > 0$, $u^*(t)$ is as small as possible, namely

$$\min_{u(t)\in[U_{min},\ U_{max}]} \lambda^{*'}(t)Bu(t) = \lambda^{*'}(t)BU_{min}$$

If $\lambda^{*'}(t)B < 0$, $u^*(t)$ is the greatest possible, namely

$$\min_{u(t)\in[U_{min},\ U_{max}]} \lambda^{*'}(t)Bu(t) = \lambda^{*'}(t)BU_{max}$$

The optimal control $u^*(t)$ is thus described by the following function:

$$u^*(t) = \begin{cases} U_{min} & \text{if } \lambda^{*'}(t)B > 0 \\ U_{max} & \text{if } \lambda^{*'}(t)B < 0 \\ \text{undetermined} & \text{if } \lambda^{*'}(t)B = 0 \end{cases} \tag{13}$$

For the existence, uniqueness and normality (no indeterminability) of this control, one can use the following theorem:

Theorem 2. (Naidu (2002)) If system (3) is fully controllable then there is a unique minimum time control which is solution of problem (5). This command is also normal, i.e.,

$$\nexists\ T_2 > T_1,\ [T_1,\ T_2] \subset [0,\ T_f] \quad \text{such that } \lambda^{*'}(t)B = 0\ \forall t \in [T_1,\ T_2]$$

By denoting $\lambda^*(t) = [\lambda_1^*(t)\ \lambda_2^*(t)\ \lambda_3^*(t)\ \lambda_4^*(t)\ ]'$, we can also note that because of the particular structure of B, (13) can be written as

$$u^*(t) = \begin{cases} U_{min} & \text{if } \lambda_1^*(t) > 0 \\ U_{max} & \text{if } \lambda_1^*(t) < 0 \end{cases} \tag{14}$$

Finally, note that the initial values of the state variables are given but the initial values of costate vector λ^* are unknown. To simplify the choice of initial values of the components of the costate vector, we use the fact that the Hamiltonian should be equal to zero at any point of the optimal trajectory (condition (10) of Pontryagin's theorem). If we also note that for an initial condition $x(0) = -x_e < 0$ and a final condition $x_f(T_f) = 0$, the initial value of the control (the flow rate injection of drugs u_{an}) must be positive, it follows that $u(t = 0^+) = U_{max}$. Then at $t = 0^+$, we have $\lambda_1^*(0^+) < 0$ and $\lambda^*(0^+)$ must verify:

$$H\Big|_{t=0^+} = 1 + \lambda^*(0^+)(-Ax_e + BU_{max}) = 0 \tag{15}$$

Given that $Ax_e + Bu_e = 0$ and $U_{min} = -u_e$, it follows that:

$$\lambda_1^*(0) = \frac{-1}{U_{max} - U_{min}} \tag{16}$$

3.3 Computation algorithm

The initial value of the other components of the costate vector is unknown. An iterative approach likely to solve problem (5), summarized by the diagram in Figure 3, is expressed as follows:

Step 1: Compute $\lambda_1^*(0)$ as in (16) and select a value for the initial condition $\lambda_2^*(0)$, $\lambda_3^*(0)$, $\lambda_4^*(0)$.

Step 2: Compute $\lambda^*(t) = e^{-A't}\lambda^*(0)$ on a sufficiently long interval $[0,\ T]$.

Step 3: Using the costate $\lambda^*(t)$, evaluate the control $u^*(t)$ defined in equation (14).

Step 4: Compute the associated trajectory $x^*(t)$ for the control evaluated at the previous step on the interval $[0\ T]$.

Step 5: Monitor the trajectory $x^*(t)$ and find

a) If there exist $t = T_f \in [0\ T]$ such that

$$\frac{\|x_f(T_f)\|}{\|x_{fe}\|} \leq \varepsilon \tag{17}$$

with ε : a chosen precision threshold and $x_{fe} = [-x_{e1} \quad -x_{e4}]$, then the solution of (5) is given by T_f and u^* is the minimum time control of the bang-bang form.

b) If not, change the initial value of $\lambda^*(0)$ and repeat the previous steps until the satisfaction of the stop criterion (17). The change of the initial value can be performed according to a Newton gradient method, for example.

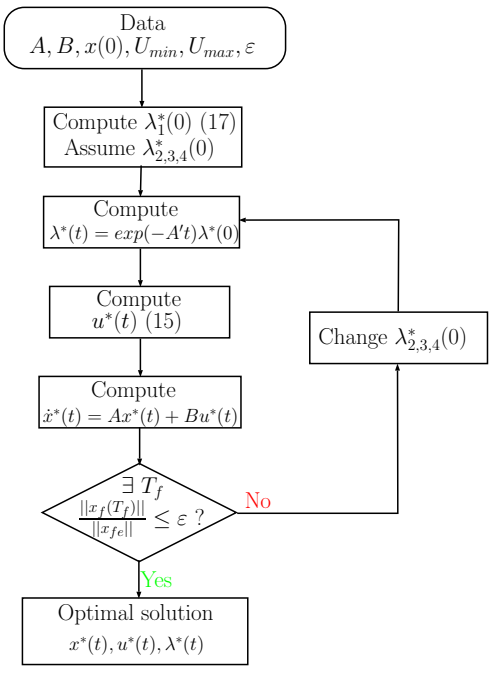

Fig. 3. Flowchart for the computation of the optimal control solution to Problem (5)

4. NUMERICAL EXAMPLE

Let us consider as a nominal patient a man of 53 years, 177 cm and 77 kg. The equilibrium point and the flow rate

corresponding to a BIS of 50 are :

$$x_{e1} = 14.51mg, \quad x_{e2} = 64.26mg, \quad x_{e3} = 809.2mg,$$
$$x_{e4} = 3.4mg/l, \quad u_e = 6.08mg/min$$

System (3) centered on this equilibrium point is defined with

$$A = \begin{bmatrix} -0.9170 & 0.0683 & 0.0035 & 0 \\ 0.3021 & -0.0683 & 0 & 0 \\ 0.1958 & 0 & -0.0035 & 0 \\ 0.1068 & 0 & 0 & -0.4560 \end{bmatrix}, \; B = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

and $u \in [U_{min}, \; U_{max}]$, $U_{min} = -u_e$, $U_{max} = 100mg/min$.

We are seeking for the minimum time control that can bring the patient from its initial awake state $x = -x_e$ to a final state where the fast states $x_f(T_f) = 0$. The final condition of the slow states is free. $\lambda_1^*(0)$ can be computed using (16) which gives $\lambda_1^*(0) = -0.0094$. The other components of the costate vector are computed by the iterative procedure presented in Figure 3. The algorithm is programmed under MATALB with the use of the *fsolve* function which uses the Newton gradient method to change the value of $\lambda^*(0)$. It is important to note that the convergence to a solution is very sensitive to the choice of the initial values of $\lambda_2(0)$, $\lambda_3(0)$ and $\lambda_4(0)$. By setting the precision threshold ε at 10^{-4}, the initial value of the costate vector corresponding to the optimal solution is $\lambda^*(0) = [-0.0094 \; -0.0019 \; -0.0450 \; -0.0400]'$ and the minimum time is estimated at $T_f = 1.85 \; min$ when the stop criterion reached $\frac{\|x_f(T_f)\|}{\|x_{fe}\|} = 1.68 \times 10^{-5}$. The minimum time control and the variation of $\lambda^{*'}(t)B$ are plotted in Figure 4 while the corresponding trajectory of the fast states is given in Figure 5.

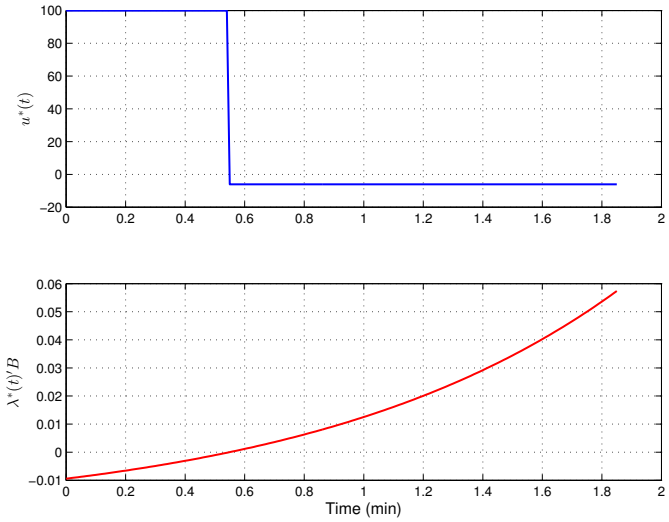

Fig. 4. The minimum time control, $u^*(t)$ in mg/min, solution to Problem (5) and the evolution of $\lambda^*(t)B$.

For this nominal patient, the optimal control allowing the fast states of system (3) to reach the origin from an initial state $x = -x_e$ i.e., allowing the fast states of system (1) to reach their equilibrium point $x_{an} = x_e$ starting from an initial state $x_{an} = 0$, consists at injecting the maximum flow rate of propofol for 0.55 minutes (about 35 seconds) followed by a zero flow for 1.3 minutes. Figure 6 shows the corresponding evolution of the BIS.

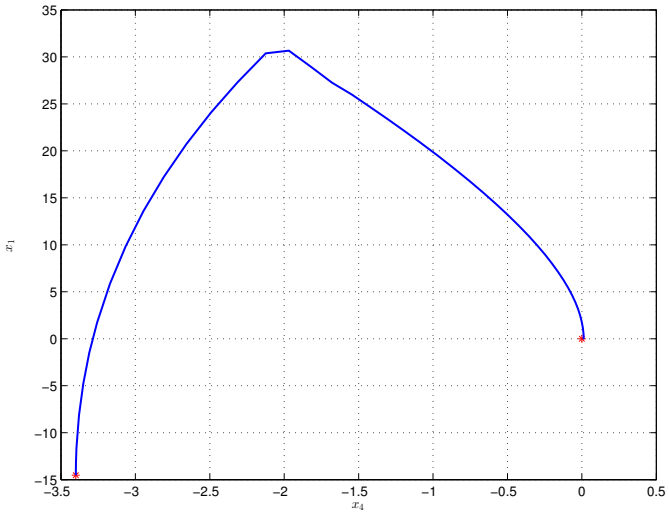

Fig. 5. The optimal trajectory of fast states to reach $x_f(T_f) = 0$ corresponding to the minimum time control $u^*(t)$.

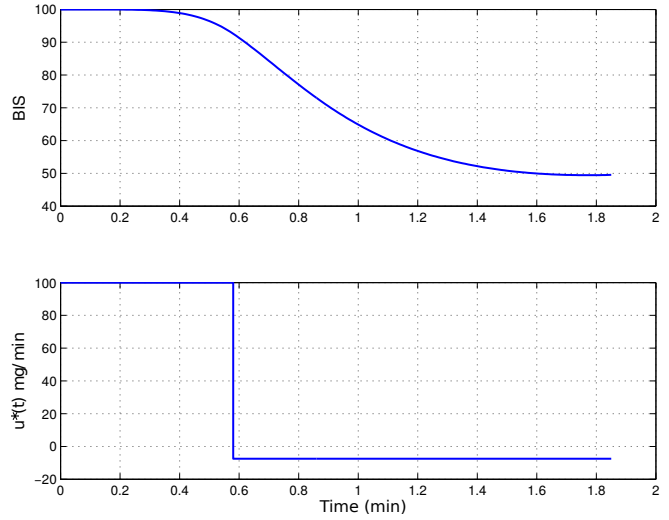

Fig. 6. The BIS evolution in response to the minimum time control $u^*(t)$ which consists at keeping $u(t)$ at its maximum $U_{max} = 100mg/min$ for about 0.55 minutes then switch to its minimum $U_{min} = -u_e$ for 1.3 minutes.

The slow states x_{an2}, x_{an3} are guaranteed to stay in the positive orthant as long as u_{an} remains positive but there is no condition on their final value. Figure 7 presents the evolution of the slow states (x_2, x_3) which supports the approach of splitting fast and slow states. If the slow ones were also considered in the terminal constraint of the time optimal control, it would require a huge time to reach this optimum without any influence on the BIS.

Once the equilibrium target is reached, or, at least, a neighbourhood, we can switch to a closed loop control in order to maintain the system close to this equilibrium. The slow states can be considered as disturbances. The stability of the full strategy will be guaranteed as soon as the switch occurs once the trajectory of the system has

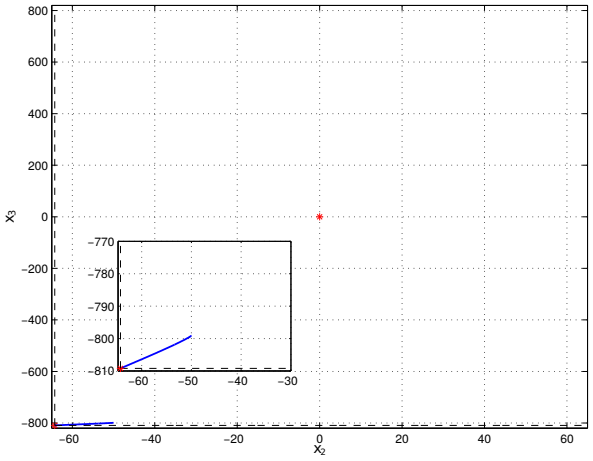

Fig. 7. The trajectory of the slow states corresponding to $u^*(t)$.

entered an invariant domain around the equilibrium (Zabi et al. (2015)).

5. CONCLUSION

In this paper, we presented an optimal control strategy to emulate the strategy implemented by the anaesthesiologists with an initial injection of a big amount of drugs (bolus) for a short time, followed by a phase without adding drug ($u_{an} = 0$) before switching to a manually control corresponding to the maintenance phase. This type of result is also obtained using invariant sets theory in Fiacchini et al. (2016).

The minimum time control computed aims at transferring the patient from its awake state to the final state corresponding to a BIS of 50. Since the patient model is composed of slow and fast dynamics and the BIS is function of the fast ones, we considered the final state of the optimal control as only that one of the fast dynamics. The optimal control $u^*(t)$ is patient dependent and could be transformed as a standard protocol exactly as it is done manually by the anesthesiologist to select the bolus and the duration of injection for each patient depending on its characteristics.

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