Adaptive Controller Using Fixed Point Transformation for Regulating Propofol Administration Through Wavelet-based Anesthetic Value

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***Abstract*—In recent years automated anesthesia has gained much interest. In this paper the applicability of the Fixed Point Transformation-based Adaptive Control design for automatic control of the depth of hypnosis during surgical operation has been investigated. The applied control design assumes the availability of the rough model of the dynamic system under control. The here presented technique regulates the WAV_{CNS} index as the only measurable variable by controling the intravenous propofol administration. Simulation results validate that the proposed control design ensures promising performance and is able to cope with unexpected surgical stimulations and anesthetic interactions during surgical procedures.**

***Index Terms*—Anaesthesia Models, Wavelet-based index, Propofol Administration, Fixed Point Transformation-based Adaptive Control.**

I. Introduction

Several surgical procedures need general anesthesia for meeting critical requirements in order to ensure the proper level of unconsciousness, muscle relaxation to avoid unwanted muscle movement, block the sensation of pain, etc. [1]. For this purpose various modern drugs as, for e.g. *Propofol* (a hypnotic drug) and *Remifentanil* (an analgesic drug having respiratory depressant effects), and their effects have been widely documented [2], [3], [4], [5]. Numerous studies have been carried out regarding the propofol administration during general anaesthesia and the WAV_{CNS} index [6] . The maintenance of the *"Depth of Hypnosis"* (DoH) is a control task that aims modeling the effect of the applied drug interaction [7]. Widely accepted methods for measuring the DoH are the BIS (Bispectral Index), RE (response entropy) and the WAV_{CNS} index. Adaptive control of anaesthesia helps avoiding several undesired effects such as overdosing, underdosing, weak response for unexpected surgical stimulations, etc. Many control methodologies have been introduced regarding the propofol administration [7]. Most of them rely on traditional state-feedback concept [8]. The main difficulty of this task is that the precise values of the model parameters relating the measureable WAV index to the state variables are not available, thus the classical model-based observes can not be used [9], [10]. This paper focuses on the propofol administration through WAV_{CNS} models [6] combined with the Robust Fixed Point Transformation-based control approach. In comparision with the available control strategies for this problem in the literature, the main advantage of the here presented technique is that it does not require complicated estimation procedures. The WAV_{CNS} index represents the necessary measurable variables that is strictly related to the control aim. This signal measures the brain activity (EEG) of the patient [8]. The here described control design also accounts for the pharmacokinetic (PK) and pharmakodynamic (PD) inter-individual variability [11]. Simulation results validate the applicability of the presented approach.

II. Model for Personalized Propofol Administration

A. The Pharmacokinetic-Pharmacodynamic (PKPD) and the Wavelet-based Anesthetic Value (WAV) Modeling

In recent years the PK-PD (pharmacokinetic-pharmacodynamic) modeling has been widely used for describing the relationship between the drug doses, concetrations and drug effects over the time. In the present

paper we used the same model that was derived by [11] and described by a series of connection of PK and PD and WAV monitor model. The scheme of the model can be seen in Fig. 1. This model discerns four compartments in

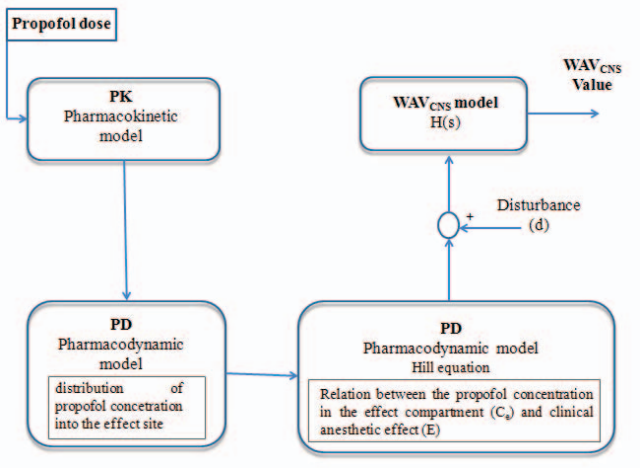

Fig. 1. The scheme of the patient model

the patient's body as follows: 1) plasma, 2) fast peripheral compartments, 3) slow peripheral compartments and 4) a hypothetical *"effect site compartment"* that is used for representing the delay between the plasma drug concentration and the observable drug response. The *"state variables"* are the x_i, $i \in \{1,2,3,4\}$ propofol concentrations in the appropriate compartments in mg/L units. The 4^{th} equation pertains for the effect site compartment. The equations of motion of the dynamic system are given in (1) in which the *"control signal"* is the intravenous propofol injection rate u in mg/min units. Evidently, the coefficients k_{10}, k_{21}, k_{31} and k_4 have the dimension of min^{-1} and describe decay rates of the drug in the appropriate compartments while the other ones correspond to exchange rates between the compartments. The parameters can be calculated according to Table I taking into account the patient's individual parameters, such as gender, age, etc. Though *at least "in principle"* x_1, x_2, $x_3\, x_4 \geq 0$ could be directly measurable, in the practice we have information only on the drug injection rate u. From the point of view of control technology the main problem is that x_4 cannot be measured directly. It is related to a directly measurable actual *"WAV_{CNS} index"* by a strongly nonlinear function (the so called Hill curve) that also contains patient-dependent parameters (3). The Hill equation has been originally developed to describe the relation between oxygen tension and the saturation of haemoglobin and today in pharmacology it has been extensively used. The PK model is described as follows [11], with the C_p plasma concentration as output:

$$\dot{x}_1 = -\left(k_{10} + k_{12} + k_{13}\right) x_1 + k_{21} x_2 + k_{31} x_3 + \frac{u}{V_1} \ , \quad \text{(1a)}$$

$$\dot{x}_2 = k_{12} x_1 - k_{21} x_2 \ , \quad \text{(1b)}$$

$$\dot{x}_3 = k_{13} x_1 - k_{31} x_3 \ , \quad \text{(1c)}$$

$$C_p = x_1, \quad \text{(1d)}$$

where V_1 is the volume of plasma compartment and $u = [I_j, k_{ij}]$ contains the rate constants. The PD model represents the delay of the propofol distribution to the effect site, given by

$$x_4(s) = C_e(s) = e^{-T_d s} \frac{k_a}{s + k_d} C_p(s), \quad (2)$$

in which the transport delay and the rate of propofol distribution is denoted by T_d, k_a and k_d. Further, the relation between C_e (the concentration in the effect site compartments) and the clinical anesthetic effect $E = E(C_e)$ is defined with the Hill equation as:

$$E(C_e) = \frac{[\hat{C}_e]^\gamma}{1 + [\hat{C}_e]^\gamma}, \quad (3)$$

where γ denotes the receptiveness of the patient to the drug, and $\hat{C}_e = \frac{C_e}{E_{50}}$, while E_{C50} is the necessary concentration of the drug to reach the half maximal effect.

TABLE I
THE PARAMETERS OF THE ANAESTHESIA MODEL

Parameter	Calculation
$V_1\,[L]$	4.27
$V_2\,[L]$	$18.9 - 0.391(\text{age}\ [year] - 53)$
$V_3\,[L]$	2.38
lbm for males in [12]	$1.1\text{weight}\ [kg] - 128\frac{\text{weight}\ [kg]^2}{\text{height}\ [cm]^2}$
lbm for females in [12]	$1.07\text{weight}\ [kg] - 148\frac{\text{weight}\ [kg]^2}{\text{height}\ [cm]^2}$
$C_{l1}\ \left[\frac{L}{min}\right]$	$1.89 + 0.0456\,(\text{weight}\ [kg] - 77)$ $-0.0681\,(\text{lbm}\ [kg] - 59)$ $+0.0264\,(\text{height}\ [cm] - 177)$
$C_{l2}\ \left[\frac{L}{min}\right]$	$1.29 - 0.024\,(\text{age}\ [year] - 53)$
$C_{l3}\ \left[\frac{L}{min}\right]$	0.836
k_{10}, k_{12}, $k_{13}\ \left[min^{-1}\right]$	$\frac{C_{l1}}{V_1}$, $\frac{C_{l2}}{V_1}$, $\frac{C_{l3}}{V_1}$
k_{21}, $k_{31}\ \left[min^{-1}\right]$	$\frac{C_{l2}}{V_2}$, $\frac{C_{l3}}{V_3}$
$E_{C50}\ \left[\frac{mg}{L}\right]$	patient-dependent
$\gamma\,[dimless]$	patient-dependent

The formulae were taken from [1] with the exception of those that are marked by [12] The term "lbm" denotes the "Lean Body Mass" that is a component of body composition, originally calculated by subtracting body fat weight from total body weight in $[kg]$ units.

The WAV sensor model technology has been derived by [6] and has been used for characterizing the non-stationary electophysiological signals that is able to detect the change in the patient's state. The WAV_{CNS} and the WAV_{ANS} are the two main applications of the Wavelet-based Anesthetic Value technology. The first quantifies the CNS (Central Nervous System) depression while the latter quantifies the ANS (Autonomic Nervous System) depression using ECG analysis.

In this paper, for the patient model we use the WAV_{CNS} index, that is a dimensionless value between 0 and 100. The 0 value stands for the deep hypnosis state and 100 means the total conscious patient. The recommended value during surgery is between 40 and 60 in order to avoid both overdosing and intra-operative awareness. In comparision with the commonly used BIS (bispectral index) the WAV_{CNS} utilizes the time-frequency localization of wavelets. Therefore also the phase and frequency shifts can be well detected in the electroencephalogram (EEM) signals. For limiting the measurement noises and for eliminating the high frequency components the following model has been proposed using a second order IIR filter. The model for measuring the propofol drug effect is given by [6],

$$y(s) = WAV_{CNS}(s) = H(s)[E(s) + d(s)] = \\ = 100\left[\left[1 - \frac{1}{(8s+1)^2}\right][E(s) + d(s)]\right] \quad (4)$$

that also reflects the effects of anesthesia drug and unknown surgical stimulation denoted by $d(s)$. In the sequel the properties of the above model are investigated from the point of view of the adaptive control.

B. Combinatin of the PKPD Modeling with the Robust Fixed Point Transformation-based Adaptive Control

Since $x_4(t)$ in (1) cannot be directly measured it is expedient to develop an equation of motion for the directly measurable variable $WAV_{CNS}(t)\,[dimless] \in [0, 100]$. The equations in (1) reveal that $\dot{x}_4(t)$ is not directly related to the control signal $u(t)$. However, in the time-derivative of (1d) the quantity $\dot{x}_1(t)$ appears that is directly related to the control signal u by (1a). Therefore we have to develop an equation for $\ddot{E}(C_e)(t)$ in which the control signal u is present. Furthermore, also the delay of the propofol distribution to the effect site has been taken into consideration with $T_d = 5[s]$, as follows

$$\dot{E}(t) = \frac{dE}{d\xi}\frac{d\xi}{dt} = E'(\xi(t - T_d)\dot{\xi}^2) \ , \quad (5a)$$

$$\ddot{E}(t) = E'(\xi(t - T_d)\ddot{\xi}) + E''(\xi(t - T_d)\dot{\xi}^2) \quad (5b)$$

$$E'(\xi(t - T_d)\left(k_d[-k_{10} - k_{12} - k_{13}]x_1(t) + k_{21}x_2(t) + k_{31}x_3(t) + \frac{u}{V_1}\right)_{t-T_d} = \frac{1}{100}\ddot{y} + \rho \quad (5c)$$

$$k_a x(t) + \dot{x}(t) = k_d u(t - T_d) \quad (5d)$$

in which ρ denotes some additive terms. Equation (5c) has fundamental significance in the fixed point transformation-based adaptive control. It states that $E'(\xi(t - T_d))$ is an *affine function of* u . Consequently for an increase or decrease in $E'(\xi(t - T_d))$ a decrease or increase in u is necessary independent of the actual values of $x_1(t), x_2(t), x_3(t), x_4(t))$. This control approach uses only this *a priori* information and this directly measurable signal and does not need the estimation of the state variables $x_1(t), x_2(t), x_3(t),$ and $x_4(s)$.

III. Principles of Fixed Point Transformation-based Adaptive Control

The Robust Fixed Point Transformation (RFPT) was originally introduced as an alternative of the Lyapunov function-based adaptive approach ([13], [14]). It has become clear in the recent years through simulation investigations that it can be successfully applied in adaptive optimal control of nonlinear systems (see, for e.g.[15], [16]. The core of the theory of the Fixed Point Transformation-based approach is that it transforms the problem of the calculation of the control signal into the task of finding an appropriate fixed point of a contractive map by generating an iterative sequence with this contracting map. It distinguishes the *"kinematic"* and *"dynamic"* parts of the control task by prescribing the *"desired trajectory tracking error damping"* or *"desired system response"* by using kinematic terms. On the basis of an available *"approximate dynamic model"* it compares the *desired response* r^{Des} and the *actually observed response* r^{Act} based on some kinematically expressed trajectory error reduction. In order to reduce the effects of the modeling imprecisions and unknown external disturbances it adaptively deforms the desired response as the input of the approximate model. Therefore the desired response can be obtained as the realized one. The key factor of this iteration is the *"Response Function"* that depends on the approximate model and the actual system under control as $r^{Obs} = f\left(r^{In}\right)$, because it describes the observable realized response that is obtained for the input of the approximate model r^{In}. Since in our case (5c) the *"Desired System Response"*, i.e. the response that directly can be influenced by the control signal u is $r^{Des} \equiv \ddot{E}^{Des}$. The iterative sequence can be generated as $\left\{r_0 = r_0^{Des}, r_1 = G\left(r_0, f(r_0), r_1^{Des}\right), \ldots, r_{n+1} = G\left(r_n, f(r_n), r_{n+1}^{Des}\right), \ldots\right\}$ in which for a *"Single Input – Single Output (SISO)"* system a real function $F(x) : \mathbb{R} \mapsto \mathbb{R}$ is used as

$$F(x) \stackrel{def}{=} B_c \tanh\left(a_c(x+b_c)\right) + K_c \ , \tag{5a}$$

$$r_{n+1} = G\left(r_n, f(r_n), r_{n+1}^{Des}\right) = \tag{5b}$$

$$= r_n + F\left(A_c \ \ f(r_n) - r_n^{Des}\right] + x_*\right) - x_* \ , \tag{5c}$$

in which x_* is the *attractive fixed point* of $F(x)$, i.e. $F(x_*) = x_*$. (This function has been introduced for fixed point transformation in [17].) Evidently, x_* depends on the parameters B_c, a_c, b_c, K_c, and it is easy to so set these parameters that the graph of the function defined in (5a) has only a single fixed point at which $|\frac{\mathrm{d}F}{\mathrm{d}x}| < 1$ that is satisfactory for the attractivity. If $r_n = r_\star$ for which $f(r_\star) = r_n^{Des}$ then $r_{n+1} = r_n$, therefore the fixed point of the function given in (5c) really is the solution of the control task. Normally, the kinematically formulated tracking prescription r_n^{Des} depends on the lower order time-derivatives of the controlled coordinate if it varies slowly. Therefore for the convergence of this sequence the flatness of G is necessary in the vicinity of $r_\star$. Really, at $r_\star$

$$\frac{\partial r_{n+1}}{\partial r_n}\Big|_{r_\star} = 1 + \frac{\mathrm{d}F}{\mathrm{d}x}\Big|_{x_*} A_c \, \frac{\mathrm{d}f}{\mathrm{d}r}\Big|_{r_\star} \tag{6}$$

therefore properly setting the parameter A_c the condition $|\frac{\partial r_{n+1}}{\partial r_n}| < 1$ can be guaranteed.

IV. Simulation Results

The values used for the *"approximate model parameters"*are given in Table 1 [12] that consists of six male and one female patients data as *age=38 year*, *height=169 cm*, *weight=65 kg*, *gender=male*, E_{C50}*=7.42 mg/L*, E_0*=93.1*, and γ*=3*. For the "kinematic part" various trajectory tracking strategies can be prescribed to track the *"nominal trajectory"* denoted by the superscript N. For e.g.,the desired $\ddot{W}AV_{CNS}^{Des}$ can be obtained by using a PD-type control prescribing the equation $\left(\Lambda + \frac{\mathrm{d}}{\mathrm{d}t}\right)^2 \left[WAV_{CNS}^N(t) - WAV_{CNS}(t)\right] \equiv 0$ with a constant $0 < \Lambda \in \mathbb{R}$ or a PID-type controller with using the equation $\left(\Lambda + \frac{\mathrm{d}}{\mathrm{d}t}\right)^3 \int_{t_0}^t \left[WAV_{CNS}^N(\xi) - WAV_{CNS}(\xi)\right] \mathrm{d}\xi \equiv 0$. The unexpected effects during the surgical operation has been represented with the disturbance values in the signal according to [18]. The following control parameters were used in the simulation:

TABLE II
The control parameters

Parameter	Value
Λ	$1\,min^{-1}$
B_c	$100\,dimless$
a_c	$\frac{1}{2\lvert B_c\rvert}\,dimless$
b_c	$2\,dimless$
K_c	$0\,dimless$
A_c	$-0.25\,min^2$
δt WAV_{CNS} sampling time	$5/60\,min$

The results presented below belong to Patient 1 who had the following relevant parameters: *age=40 year*, *height=163 cm*, *weight=54 kg*, *gender=male*, E_{C50}*=6.33 mg/L*, E_0*=98.8*, and γ*=2.24*. At the short initial phase 30 $\frac{mg}{min}$ propofol injection rate was applied without any control effort to give a more easily manageable propofol concentration level to the adaptive controller. The control parameters were set for Patient 1 by manual trial-and-error procedure. The results have also revealed that the PD-type kinematic error relaxation strategy has given the best results in the adaptive controller.

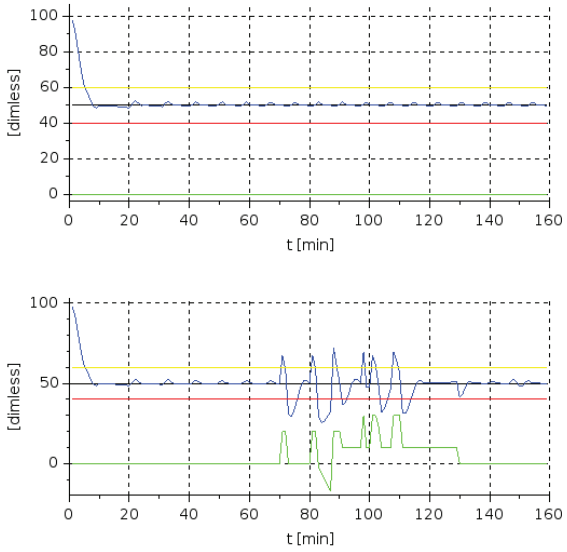

Fig. 2. The "Nominal" (black), and the "Realized" (blue) WAV_{CNS} values for the disturbance-free (top) and disturbed (bottom) cases for Patient 1 (the disturbance signal is denoted by green line, while the desired upper and lower limits of the WAV_{CNS} Index) denoted by the yellow and the red lines

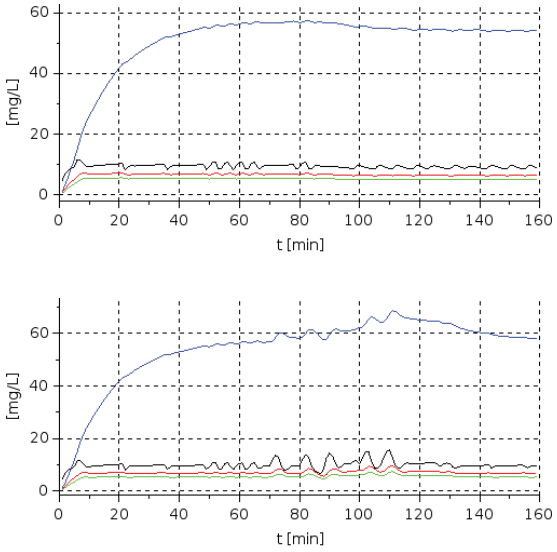

Fig. 3. The state variables (i.e. Propofol concentration) vs. time for the disturbance-free (top) and disturbed (bottom) cases for Patient 1 (x_1: black, x_2: blue, x_3: green, and x_4: red lines)

In Fig. 2 the WAV_{CNS} values are described in time. It can be observed that in the disturbance-free case the signal has a

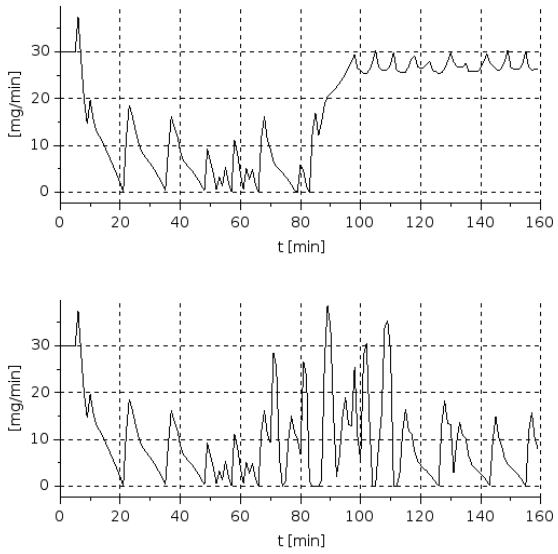

Fig. 4. The control signal (i.e. Propofol injection rate) vs. time for the disturbance-free (top) and disturbed (bottom) cases for Patient 1

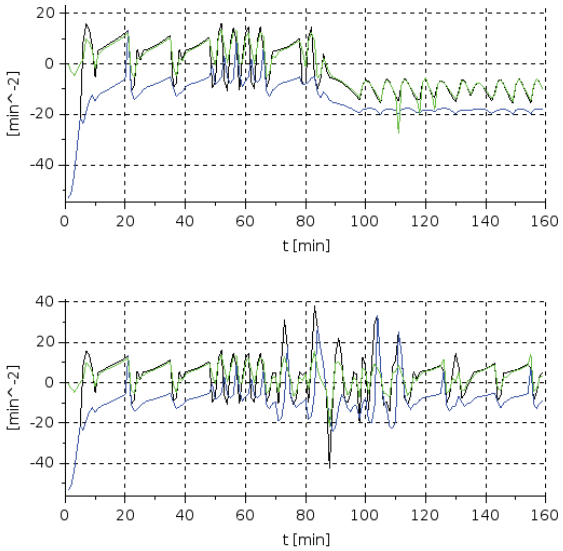

Fig. 5. The $\ddot{W}AV_{CNS}$ values vs. time for the disturbance-free (top) and disturbed (bottom) cases for Patient 1 ($\ddot{W}AV_{CNS}^{Des}$ "desired" value: black line, $\ddot{W}AV_{CNS}^{Def}$ "adaptively deformed" value: blue line, and the $\ddot{W}AV_{CNS}$: realized value: green line)

little oscillation around the desired value 50. The disturbances leave the recommended zone for relatively short durations. Figure 3 displays the concentration values in the various compartments while in Fig. 4 the Propofol infusion rate in time is given. The operation of the adaptivity can be seen in Fig. 5 where the "desired" and the "realized" values are close to each other and they seriously differ from the adaptively deformed values. This means that the adaptive controller can appropriately manage the weaknesses of the simple affine model, thus the complicated process of state and parameter estimations can be avoided by the simple adaptive law.

V. Conclusions

In this paper a Fixed Point Transformation-based control approach has been introduced for regulating the depth of hypnosis as measured by the Wavelet-based Anesthetic Value (WAV). The here presented technique maintains the WAV_{CNS} index by controling the intravenous propofol administration. The applied patient model contains the inter-individual PK and PD varibility. Simulation results validate that the here presented control design ensures promising performance and is able to cope with unexpected surgical stimulations and anesthetic interactions during surgical procedures. The investigations also highlight that in the Fixed-Point Transformation-based control strategy further improvments in the parameter tuning may lead to better performance.

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