PASSIVITY BASED FRACTIONAL ORDER ADAPTIVE CONTROL OF DEPTH OF ANESTHESIA

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Abstract — In this paper, a passivity based model reference adaptive controller with fractional-order adaptation mechanism is utilized for control of depth of anesthesia. The propofol infusion rate is adjusted to reach an appropriate Bispectral Index (BIS). The Pharmacokinetic-Pharmacodynamic (PK-PD) model is employed to model the distribution of propofol in patient body. Since, the PK-PD model parameters depend on physical specifications of patient, employing an adaptive controller to control this system is inevitable. The utilized controller is a pole placement controller in which its polynomial coefficients are adjusted according to a fractional-order adaptation mechanism. Simulation results on several patients demonstrate the efficiency of the proposed method in the presence of disturbance, noise, and model uncertainties.

Keywords — Model reference adaptive controller; Fractional-order adaptation mechanism; Passivity based controller; depth of anesthesia.

I. INTRODUCTION

Reducing the side effects of anesthesia during surgery requires online monitoring and control of the depth of the anesthesia (Bibian et al., 2005). Although, several indicators have been proposed to measure the depth of anesthesia in the literature, the Bispectral index (BIS) is still known as the common indicator in this area (Johansen and Sebel, 2000). Determination of the appropriate drug dose through modern control approaches requires modeling the effect of the propofol infusion on the patient body (Lan et al., 2012). Pharmacokinetic (PK) and pharmacodynamic models (PD) have been employed for mathematical modeling of the drug disposition and the drug effect on human body, respectively (Schüttler and Ihmsen, 2000).

Several control methods have been utilized to control the depth of the anesthesia in the literature. Most of these methods try to regulate the BIS value in a predefined range. Optimal PID controllers have been utilized in this area (Padula et al., 2017). Robust control approaches such as H∞ based methods have been employed for control of depth of the anesthesia (Caiado et al., 2013). Model predictive control (MPC) has been utilized in this area (Jonescu et al., 2008). Moreover, the reinforcement learning (Padmanabhan et al., 2015) and Type-2 self-organizing fuzzy logic controllers (Doctor et al., 2016) have been employed for closed loop control of anesthesia.

Adaptive control methods have been utilized to control the depth of the anesthesia. Since the PK model is a non-negative system, a Lyapunov-based adaptation mechanism giving positive control signal has been presented by Haddad et al. (2003). Hui et al. (2005) proposed a Lyapunov-Krasovskii-based adaptation mechanism for BIS regulation in the presence of unknown time delays and actuator amplitude constraints. Lyapunov-based neuroadaptive output feedback controllers for attaining a desired constant level of the depth of anesthesia in the face of noisy electroencephalographic (EEG) and input amplitude constraints have been established (Volansky et al., 2011). To increase the robustness to inter-patient variability in the anesthesia control, the L1 adaptive controllers have been constructed (Kharisov et al., 2015).

On the other hand, utilizing fractional calculus as a useful tool for modeling and control of dynamical systems has been considered by the control engineers (Podlubny, 1999). Copot et al. (2013) proposed a fractional order pharmacokinetic model for propofol diffusion in anesthesia. Dumont et al. (2009) presented the commonly Commande Robuste d’Ordre Non Entier (CRONE) controller as a fractional order controller for BIS regulation in anesthesia. Navarro-Guerrero and Tang (2017) introduced a fractional order PK-PD model that its parameters have been estimated though an identification procedure.

Fractional order adaptation mechanisms have been employed to increase the performance of adaptive controllers. In model reference adaptive control (MRAC) structure, the gradient adaptation mechanism could be modified by utilizing the fractional order derivative instead of ordinary derivative (Ladaci and Charef, 2006). The obtained fractional order adaptation mechanism leads to improvement in the transient response. Ladaci et al. (2008) introduced the fractional order adaptive high gain controllers for linear time variant systems with relative degree one. Tabatabaei (2015) employed fractional order normalized gradient adaptation rule for velocity control of a permanent Magnet Synchronous Motor (PMSM). Moreover, in his work, the fractional order Lyapunov based adaptation mechanism has been developed, too.

In this paper, a Fractional Order Passivity based MRAC (FOPMRAC) adaptation mechanism is established. In this approach, a fractional order integrator (with fractional order between (0,1]) as a passive element is employed to attain the closed loop system stability according to the passivity theorem. Numerical simulations
performed on different patients demonstrate the robust performance of the proposed fractional order adaptation rule.

The remainder of this paper is organized as follows. The patient model is introduced in Section II. A review on passivity based MRAC (PMRAC) is presented in Section III. The details of the proposed FOPMRAC are given in Section IV. The application of the proposed method for BIS regulation in anesthesia is presented in Section V. The concluding remarks are given in Section VI.

II. PATIENT MODEL

The effect of the propofol infusion rate on the patient body could be described with a Wiener PK/PD model. The Pharmacokinetic (PK) model as a three-compartment model describes the drug infusion effect on drug concentration in the body. The second compartment is the pharmacodynamics (PD) model that consists of a single compartment plus a static nonlinear-ity. In this model, the observed clinical effect is related to the drug concentration in the central component. The PK/PD model of the patient is shown in Fig. 1 (Schnider et al., 1998). The infusion rate of the propofol and the BIS considered as the input and output, respectively. Schnider et al. (1998) derived the following state space equations for the PK model

\[
\begin{align*}
\dot{x}_1 &= -(k_{10} + k_{12} + k_{13}) x_1 + (k_{21} + k_{31}) x_2 + k_{21} x_3 + \frac{1}{V_1} u, \\
\dot{x}_2 &= k_{12} x_1 - k_{21} x_2 + k_{32} x_3, \\
\dot{x}_3 &= k_{13} x_1 - k_{31} x_3,
\end{align*}
\]

where \( u \) is the infusion rate of the propofol in (mg/min) into the central compartment (blood), \( x_1 \) is the drug concentration in the central compartment (mg/L), \( x_2 \) and \( x_3 \) are the drug concentrations in the peripheral compartments. \( k_{10} \) is the elimination rate of the drug through metabolism (min\(^{-1}\)). \( V_1 \) is the volume of the \( i \)-th compartment (Lm3). \( k_{ji}, j = 1, 2, 3 \) are the drug transfer rate constant from \( i \)-th compartments to \( j \)-th component (min\(^{-1}\)). These parameters depend on patient specifications such as weight (in kilogram), height (in centimeter), lean body mass (lbm), gender (male or female), and age (in years). These parameters are given as (Schnider et al., 1998).

\[
k_{10} = \frac{C_{10}}{V_1}, k_{12} = \frac{C_{12}}{V_1}, k_{13} = \frac{C_{13}}{V_1}, k_{21} = \frac{C_{21}}{V_2}, k_{31} = \frac{C_{31}}{V_3}, k_{30} = 0.456.
\]

where

\[
\begin{align*}
V_1 &= 4.27, V_2 = 18.9 - 0.391(\text{age - 53}), V_3 = 2.38, \\
C_{10} &= 1.89 + 0.456(\text{weight - 77}) - 0.0681(\text{lbm - 59}) + 0.264(\text{height - 177}), \\
C_{12} &= 1.29 - 0.024(\text{age - 53}), C_{13} = 0.836, \\
lbm(\text{male}) &= 1.1 \text{ weight} - 128 \text{ weight}^2 / \text{ height}, \\
lbm(\text{female}) &= 1.07 \text{ weight} - 148 \text{ weight}^2 / \text{ height}.
\end{align*}
\]

Figure 1 The PK/PD compartmental model.

The effect site compartment is related to central compartment through a first order model given by

\[
\dot{C}_e(t) = k_{e0} (x_1(t) - C_e(t)),
\]

where \( k_{e0} \) is the drug elimination rate from the effect site compartment and \( C_e(t) \) is the concentration of drug in the effect site compartment. The BIS is related to \( C_e \) by the following nonlinear equation

\[
BIS(t) = BIS_0(1 - \frac{C'_e(t)}{EC_{00} + C'_e(t)}),
\]

where \( BIS_0 \) is the index value in a awake state (without drug), which is typically assumed to the value of 100. \( EC_0 \) is the drug concentration at half maximal effect and represents the patient’s sensitivity to the drug; \( \gamma \) determines the degree of nonlinearity of the function. The desired BIS value for surgery purposes is ranging from 40 to 60 (the nominal value is 50).

Considering (1) and (6), the overall transfer function of system \((G(s))\) with input \( u \) and output \( C_e \) becomes

\[
G(s) = \frac{\gamma_0 (s^2 + b_2 s + b_1)}{(s^2 + a_2 s^2 + a_1 s + a_0)(s + k_{e0})},
\]

where

\[
\begin{align*}
& a_2 = k_{10} + k_{12} + k_{13} + k_{21} + k_{31} + a_1 = k_{10} k_{21} + k_{12} k_{31} + k_{13} k_{21} + k_{31} k_{21}, \\
& k_{10} k_{21} + k_{12} k_{31} + k_{13} k_{21} + k_{31} k_{21} + a_0 = k_{10} k_{21} k_{31}, \\
& b_2 = k_{21} + k_{31}, b_1 = k_{31} k_{21}, \gamma_0 = \frac{k_{e0}}{V_1}.
\end{align*}
\]

According to (2) and (9), parameters \( k_{e0}, a_2, a_1, a_0, b_1, \) and \( b_0 \) are positive. Moreover, it could be checked that \( a_2, a_1 > a_0 \). Thus, transfer function (8) is a stable minimum phase system with relative degree 2. The PK/PD model consists of a dynamic linear part (described with Eq. 8) and a nonlinear static part (described with Eq. 7). The series connection of a linear time invariant (LTI) dynamic system with a nonlinear static system is called the Wiener model (see Fig. 2). The nonlinear part (denoted by \( f \)) is invertible. This means that by employing the inverse of the nonlinear part \((f^{-1})\), a linear controller could be utilized to control a system described with the Wiener model. Figure 3 shows the control structure (\( r \) and \( y \) are the command signal and the output, respectively).
III. A REVIEW ON PMRAC

In MRAC strategy, the controller parameters are changed according to an appropriate adaptation mechanism such that the process output \(y(t)\) track the reference model output \(y_m(t)\). Equivalently, the following relation should be satisfied
\[
\lim_{t \to \infty} e(t) = \lim_{t \to \infty} (y(t) - y_m(t)) = 0, \tag{10}
\]
where \(e(t)\) is the tracking error.

Gradient based MRAC, Lyapunov based MRAC and PMRAC are the most popular adaptation mechanism have been utilized in the MRAC structure (Astrom and Wittenmark, 1995). In this paper, PMRAC has been employed. In the following, some definitions and lemmas are given to explain the PMRAC structure.

**Definition 1.** The inner product of two signals \(x_1(t)\) and \(x_2(t)\) denoted by \(\langle x_1(t), x_2(t) \rangle\) is defined as (Astrom and Wittenmark, 1995)
\[
\langle x_1(t), x_2(t) \rangle = \int_0^\infty x_1(t)x_2(t)dt. \tag{11}
\]
According to the Parseval’s theorem, relation (11) could be written as
\[
\langle x_1(t), x_2(t) \rangle = \frac{1}{2\pi} \int_{-\infty}^{\infty} X_1(j\omega)X_2(-j\omega)d\omega. \tag{12}
\]
where \(X_1(j\omega)\) and \(X_2(j\omega)\) are the Fourier transforms of \(x_1(t)\) and \(x_2(t)\), respectively.

**Definition 2.** The 2-norm of an arbitrary signal \(x(t)\) \((\|x(t)\|_2)\) is defined as (Astrom and Wittenmark, 1995)
\[
\|x(t)\|_2 = \sqrt{\int_0^\infty x^2(t)dt}. \tag{13}
\]
All signals with finite 2-norm form the \(L_2\) space. Equivalently, \(x(t) \in L_2\) if and only if \(\|x(t)\|_2 < \infty\). It could be verified that if \(x(t) \in L_2\), then \(\lim_{t \to \infty} x(t) = 0\). This concept is employed for stability analysis in PMRAC structure. This means that the model tracking could be achieved if \(e(t) \in L_2\).

**Definition 3.** A system with input \(u\) and output \(y\) is passive if \(u, y \geq 0\) (Astrom and Wittenmark, 1995).

**Lemma 1.** Consider that \(r(t)\) is a bounded square integrable signal and \(G(s)\) is the transfer function of a passive LTI system. Then, a system with input \(u(t)\) and output \(y(t)\) with the following input-output relation is passive (Astrom and Wittenmark, 1995)
\[
y(t) = r(t)G(p)(r(t)u(t)), \tag{14}
\]
where \(p\) is the derivative operator.

**Theorem 1 (Passivity Theorem).** Consider the closed loop system shown in Fig. 4. If \(H_1\) is SPR and \(H_2\) is passive, then the closed loop system is Bounded Input Bounded Output (BIBO) stable (Astrom and Wittenmark, 1995)

The passivity theorem could be employed for stability investigation of adaptive control systems with passivity based adaptation mechanism. The passivity based MRAC is summarized in the following algorithm.

**Algorithm 1.** (Astrom and Wittenmark, 1995)

**Step 1.** Find a controller structure to attain Perfect Model Following (PMF).

**Step 2.** Consider that \(G_1(s)\) is a SPR transfer function (it is a part of the process transfer function). If the controller parameters and the true parameters are denoted by \(\theta\) and \(\theta^*\), respectively, then derive the error model as
\[
e = G_1(p)[\varphi'(t)(\theta^* - \theta)], \tag{16}
\]
where \(\varphi(t)\) is the regressor that contains input and output of the process.

**Step 3.** Employ the following adaptation rule for adjustment of the controller parameters
\[
d\theta = \gamma \varphi e, \tag{17}
\]
where \(\gamma > 0\) is the adaptation rate.

IV. FRACTIONAL ORDER PMRAC

There are different definitions for describing fractional order operators. According to the Caputo definition, the fractional order derivative of a function \(f(t)\) \((D^\alpha f(t))\) is defined as (Podlubny, 1999)
\[
D^\alpha f(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{f^{(n)}(\tau)}{(t-\tau)^{n-\alpha}} d\tau, \tag{18}
\]
where \(\alpha (n-1 \leq \alpha \leq n)\) is the fractional order and \(\Gamma(.)\) is the Gamma function.

**A. FOPMRAC adaptation mechanism**

**Lemma 3.** The fractional order integrator \((I(s)=1/s^\alpha, 0<\alpha<1)\) is a passive system.

**Proof.** Consider that the input and output of this system are denoted by \(u(t)\) and \(y(t)\), respectively. Now, according to (11) and (12), we have...
where $\xi$ and $\omega_n$ are the damping ratio and natural frequency, respectively. Moreover, $A_0(s)$ is the observer polynomial commonly used in pole placement based control structure and $\omega=\beta\omega_n$, $\beta>0$. According to the procedure presented by Astrom and Wittenmark (1995), the augmented error $\varepsilon$ is defined as

$$
\varepsilon = e_f + \frac{\gamma_0 Q}{A_m A_n}\eta,
$$

(25)

where $\gamma_0>0$ is the high frequency gain of (8). Moreover, $Q$ is selected such that $\gamma_0 Q / A_0 A_m$ is SPR (to attain this goal, $Q=A_0 A_m$ is considered). $e_f$ and $\eta$ are the filtered error and error augmentation defined as

$$
e_f = \frac{Q}{P}e, \quad \eta = \frac{1}{P_i}\theta' (p, \varphi) - \omega^2 \theta,
$$

(26)

where $P=P_1 P_2$ and $P_1$ is Hurwitz and $P_2$ is a stable monic polynomial with the same degree of $R$. In this paper, $P_1=\omega_n A_m$, $P_2=\omega_0 A_0$ are considered. The parameter vector $\theta$ and the regressor $\varphi$ are given by

$$
\varphi = 1 + \frac{1}{P(p)} \left[ p^2 u, pu, u, p y, p^2 y, p y, y \right]^T.
$$

(27)

The control signal is considered as

$$
u = -P(q^2 \theta') \theta.
$$

(29)

It could be verified that (Astrom and Wittenmark, 1995)

$$
\varepsilon = \frac{\gamma_0 Q}{A_m A_n} \theta' (\theta^* - \theta).
$$

(30)

According to Corollary, the control signal (29) with adaptation mechanism (22) leads to $\lim_{t\to\infty} \varepsilon(t)=0$. According to (22), when $\varepsilon$ tends to zero, $\theta$ tends to a constant vector. Thus, according to (26), $\lim_{t\to\infty} e_f(t)=0$. Equivalently, $\lim_{t\to\infty} e(t)=0$.

V. SIMULATION RESULTS

To apply the FOPMRAC structure proposed in the previous section for BIS regulation, the Wiener model presented in Fig. 3 should be employed. According to (7), the following relation will be obtained

$$
C_r(t) = EC_{r,0} \left( \frac{BIS_t}{BIS(t)} \right)^{\frac{1}{\gamma}}.
$$

(31)

Actually, relation (31) could be employed as $f^j$ in Fig. 3. Moreover, in relation (27), $r$ is the desired value of $C_r$ that could be calculated in terms of the desired BIS in accordance with (31). In addition, $y$ in relation (27) is $C_r(t)$ that could be obtained in terms of BIS. Finally, the overall control structure is shown in Fig. 7.

Figure 7. The overall control structure for BIS regulation.
Table 1. The physical specification of patients.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>gender</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>(\gamma)</th>
<th>EC_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>28</td>
<td>164</td>
<td>60</td>
<td>2.46</td>
<td>4.93</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>42</td>
<td>179</td>
<td>78</td>
<td>1.85</td>
<td>4.82</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>50</td>
<td>163</td>
<td>83</td>
<td>2.18</td>
<td>6.44</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>40</td>
<td>163</td>
<td>54</td>
<td>2.24</td>
<td>6.33</td>
</tr>
</tbody>
</table>

Figure 8. The closed loop responses of BIS.

Figure 9. The propofol infusion rates.

To verify the performance of the proposed method, four different patients that their physical specifications are given in Table 1 are considered (Ionescu et al., 2008). The desired BIS is considered as 50. The controller parameters are considered as \(\omega_n=2\), \(\zeta=1.8\), \(\beta=0.12\), \(\alpha=0.8\) and \(\gamma=1000\).

The BIS values for the mentioned patients are shown in Fig. 8. It is obvious that the BIS for all patients could track the reference model output. This demonstrates the robust performance of the controller. Moreover, as could be seen from Fig. 9, the propofol infusion rates for these patients have admissible values. To compare the effect of the fractional order in the adaptation mechanism, the BIS responses are compared for the fractional order (\(\alpha=0.8\)) and integer order (\(\alpha=1\)) in Fig. 10 (considering similar values of \(\gamma\)). As could be seen from Fig. 10, the transient response of the BIS with fractional-order adaptation mechanism is faster comparing with the integer order one. To verify the effect of the measurement noise, a Gaussian noise with zero mean and variance 10 is added to the BIS value. Moreover, a constant disturbance with amplitude 10 is added to the output in \(t=30\) min. As could be seen from Fig. 11, the effect of the disturbance and the measurement noise is considerably attenuated.
In the control block diagram shown in Fig. 7, the inverse of the nonlinear term is utilized. However, the parameters $\gamma$ and $EC_{50}$ could vary for different patients. To investigate the effect of uncertainty in these parameters, in simulation shown in Fig. 12, the nominal response (without uncertainty in these parameters) is compared with the response obtained with uncertainty in these parameters. In other words, the mean of parameter $\gamma$ ($\gamma=2.18$) and the mean value of $EC_{50}$ ($EC_{50}=5.63$) for all patients are selected for the inverse part. Figure 12 shows that the effect of this uncertainty on the BIS responses is negligible.

VI. CONCLUSIONS
In this paper, the passivity based MRAC with a fractional order adaptation mechanism is presented. The passivity Theorem is employed for stability analysis of the proposed controller. The proposed FOMRAC is employed for BIS regulation during anesthesia. The simulation results on patients with different physical properties demonstrate the robust performance of the proposed method. Moreover, the capability of the mentioned method in disturbance and noise rejection is verified through numerical simulations.

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