An adaptive controller for propofol in anesthesia under synergistic remifentanil disturbances

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Abstract

An adaptive controller for propofol administration relying on a minimally parameterized SISO Wiener model for the depth of anesthesia is proposed. The exact linearization of this minimal Wiener structure using the continuous-time model parameters estimated online by an extended Kalman filter is a key point in the design. A linear quadratic Gaussian controller is developed for the exactly linearized system. The depth of anesthesia is considered to be measured by the bispectral index. Excellent results were obtained when the robustness of the proposed controller with respect to inter and intrapatient variability was assessed through simulations on a database of 500 patients. The closed-loop system showed good disturbance rejection properties when the synergistic effect of remifentanil in the depth of anesthesia was considered.

1 INTRODUCTION

This report presents an adaptive controller for propofol administration in anesthesia. A minimally parameterized SISO Wiener model is used for the controller development. The controlled input is the propofol rate and the controlled output is the depth of anesthesia (DoA), when quantified by the bispectral index (BIS) [1].

An intrinsic feature of drug delivery in anesthesia is the high uncertainty in the effect of drugs in the patients’ body. This is evident when standard population pharmacokinetic/pharmacodynamic (PK/PD) models are used to guide drug infusions [2, 3]. If manual control is carried out, anesthetists are

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normally able to overcome the interindividual variability by tailoring the drug administration to the patients’ needs. The key question is: how can automatic drug delivery systems mimic this ability? Automatic drug delivery has already shown to present some benefits over manual administration [2]. Whereas robust techniques might tend to perform poorly because they are designed for the “worst situation” [4, 5], adaptive schemes, on the other hand, rely on the excitation properties of the input signals. This constitutes a technical challenge since the excitation properties of drug dose profiles are, in general, poor [6]. Therefore, for propofol administration, a common practice is to partially identify the model [7] and/or to run the identification algorithms during the initial induction/transient phase. The inputs are there more excitatory, and the obtained parameter estimates can be used for offline controller design [8]. The performance of these strategies might however worsen when the dynamics of the drug distribution or effect change during the anesthetic procedure. The adaptive controller presented in this report overcomes exactly this weakness by recursively identifying the model parameters during the whole anesthesia time. Justified by the input signal excitation problems in this clinical application, a minimally parameterized model is the key to describe the nonlinear anesthetic effect of propofol in the human body, as in [9]. The adaptive controller structure uses the parameter estimates to update the control law online and to exactly linearize the Wiener structure.

The controller performance is evaluated on a database of 500 simulated patients and tested for disturbance rejection by considering the synergistic effect of remifentanil in the DoA.

The remainder of this report is organized as follows. Section 2 describes the minimally parameterized model for the DoA. Section 3 presents the adaptive controller while section 4 describes how the controller performance was assessed. Section 5 shows the results, and Section 6 presents the conclusions.

2 A MINIMALLY PARAMETERIZED WIENER MODEL

A third-order continuous-time model is used for the system linear dynamics. In the frequency domain, the dynamics is modeled by

$$Y_i(s) = \frac{\chi}{(s + \chi)} \frac{d_1 \chi}{(s + d_1 \chi)} \frac{d_2 \chi}{(s + d_2 \chi)} U_p(s),$$

where $Y_i(s)$ is the Laplace transform of the output $y_i(t)$ of the linear block of the Wiener model; $U_p(s)$ is the Laplace transform of the propofol infusion rate $u_p(t)$ (input signal); $d_1 = 9$ and $d_2 = 10$ as in [9]; and $\chi$ is the parameter to be identified online.

Following [6], and starting with the $E_{\text{max}}$ model in [10], the static nonlin-
earity used to model the effect is given by
\[ y(t) = r(\zeta, y(t)) \equiv E_0 \frac{C_{50}^\zeta}{C_{50}^\zeta + (y(t))^\zeta}, \]  
(2)

where \( y(t) \) is the output of the nonlinearity (DoA); \( C_{50} = 10 \); \( E_0 = 97.7 \) (for BIS) is the baseline effect; and \( \zeta \) is the parameter to be identified online.

The total number of patient-dependent parameters in the minimally parameterized model is hence only two and the parameter vector becomes
\[ \theta = [\chi \quad \zeta]^T. \]  
(3)

3 ADAPTIVE CONTROLLER

3.1 Structure

The structure of the adaptive controller is shown in Fig. 1. It performs three main tasks in order at each time step: online identification of the model parameters by an extended Kalman filter (EKF), exact linearization of the model using the current estimate of the nonlinear parameter, and linear adaptive control.

![Figure 1: Adaptive controller for propofol administration.](image)

3.2 Recursive identification

In order to implement the model structure (1), (2) in the EKF, the continuous-time representation (1) was sampled using a zero-order hold method [11]. Since data from the DoA indices is usually monitored every 5 seconds in the surgery environment, the zero-order hold method uses \( h = 1/12 \) min\(^{-1}\). The discrete-time model becomes
\[
\begin{align*}
x(kh+h) &= \Phi(\chi) \, x(kh) + \Gamma(\chi) \, u_p(kh), \\
y(kh) &= C(\chi) \, x(kh).
\end{align*}
\]  
(4)

where \( u_p(kh) \in \mathbb{R} \) is the piecewise constant propofol dose; \( x(kh) \in \mathbb{R}^{3 \times 1} \) is the discrete-time state-vector; \( y(kh) \in \mathbb{R} \) is the discrete-time output of the linear block; and \( \Phi(\chi) \in \mathbb{R}^{3 \times 3} \) and \( \Gamma(\chi) \in \mathbb{R}^{3 \times 1} \) are the sampled system matrices. Note that \( d_1 \) and \( d_2 \) are not shown explicitly in (4) since they are fixed in the simulations.
The sampling does not affect the nonlinear block, hence (2) can be used as it is:
\[
y(kh) = r(\zeta, y_l(kh)) \equiv E_0 \frac{C_{\zeta 0}}{C_{\zeta 0} + (y_l(kh))^2}.
\] (5)

To describe the EKF, the underlying general discrete-time nonlinear model in e.g. [12] is used. To enable the estimation of the model parameters with the EKF, an augmented identification model is defined. The augmented model merges the sampled model (4) and a random walk model for the parameter estimates [13] as
\[
\varphi(kh + h) = \begin{bmatrix}
\Phi(\chi(kh)) & 0 \\
0 & I
\end{bmatrix}
\begin{bmatrix}
x(kh) \\
\chi(kh) \\
\zeta(kh)
\end{bmatrix} + \begin{bmatrix}
\Gamma(\chi(kh)) \\
0
\end{bmatrix} u_p(kh) + \begin{bmatrix}
v_x(kh) \\
v_{\chi}(k) \\
v_{\zeta}(kh)
\end{bmatrix},
\]
\[
y(kh) = E_0 \frac{C_{\zeta 0}^{\zeta (kh)}}{C_{\zeta 0}^{\zeta (kh)} + (C(\chi(kh))\varphi(kh))^{\zeta (kh)}} + e(kh),
\] (6)
\[
\overline{C}(\cdot) = \begin{bmatrix} C(\cdot) & 0 & 0 \end{bmatrix}.
\] (7)

### 3.3 Exact linearization

Both the measured DoA (output \(y\)) and the reference value \(y_{ref}\) are exactly linearized through \(r^{-1}\) [14] (see Fig. 1) using the current estimate of \(\zeta\) provided by the EKF. The linear part of the controller is therefore designed to control the output of the linear dynamic part of the system as if there was no static nonlinearity.

### 3.4 Linear quadratic Gaussian controller

After exactly linearizing the Wiener model, an optimal regulator for the system (4) can be designed. The feedback is given by
\[
u(kh) = -L(kh) \hat{x}(kh|kh-h),
\] (8)
where \(\hat{x}(kh|kh-h)\) is the estimated vector in (4); and \(L(kh)\) is the solution to the discrete-time Riccati equation [12]. The corresponding loss function is
\[
l(x, u) = x^T(Nh)Q_0 x(Nh) + \sum_{n=0}^{N-1} x^T(nh) u^T(nh) \begin{bmatrix} Q_1 & Q_{12} \\
Q_{21} & Q_2 \end{bmatrix} \begin{bmatrix} x(nh) \\
u(nh) \end{bmatrix},
\] (9)
where the symmetric weighting matrices satisfy the positively conditions in [12, pp. 319].

Since the reference signal \(y_{ref}\) has to be followed without any static error, a slow integral action is added to (8) in order to regulate away modeling errors. The control law becomes
\[
u(kh) = -L_1(kh) \hat{x}(kh|kh-h) - L_2(kh) \sum_{n=0}^{N} (y_l(nh) - y_{ref}^l(nh)),
\] (10)
where
\[
\mathbf{L}(kh) = \begin{bmatrix} L_1(kh) & 0 \\ 0 & L_2(kh) \end{bmatrix}
\]
(11)
is obtained by solving the Riccati equation for the augmented state model
\[
z(kh + h) = \begin{bmatrix} \Phi(\hat{x}(kh)) & 0 \\ C(\hat{x}(kh)) \end{bmatrix} z(kh) + \begin{bmatrix} \Gamma(\hat{x}(kh)) \\ 0 \end{bmatrix} u(kh) + \begin{bmatrix} 0 \\ -I \end{bmatrix} y^\text{ref}_t(kh),
\]
with \( z(kh) = [x^T(kh) \ w^T(kh)] \). The additional state
\[
w(kh) = \sum_{n=0}^{N} (y_t(nh) - y^\text{ref}_t(nh))
\]
(12)
corresponds to the integral of the error in the linear loop.

To obtain an even faster servo response with respect to changes of the reference signal, the feedback is further modified to include a direct term from \( y^\text{ref}_t \), giving
\[
u(kh) = -L_1(kh) \hat{x}(kh|kh-h) + M(kh) y^\text{ref}_t(kh) - L_2(kh) \sum_{n=0}^{N} (y_t(nh) - y^\text{ref}_t(nh)),
\]
with
\[
M(kh) = (C(\hat{x}(kh))(I - \Phi(\hat{x}(kh)) + \Gamma(\hat{x}(kh))L_1(kh))^{-1}\Gamma(\hat{x}(kh))^{-1}
\]
(13)
to enforce unity static gain of the linear loop.

Due to the nature of the problem to be solved, \( u \) must be nonnegative and below a predefined maximum \( u_{\text{max}} \). The saturation in the input can be described as
\[
u_p(kh) = \begin{cases} 0, & \text{if } u(kh) < 0 \\ u(kh), & \text{if } 0 \leq u(kh) \leq u_{\text{max}} \\ u_{\text{max}}, & \text{if } u(kh) > u_{\text{max}} \end{cases}
\]
(14)

4 PERFORMANCE EVALUATION

4.1 Simulated system

In order to assess the performance of the controller in conditions that are as realistic as possible, the real patient in Fig. 1 was simulated using standard fully parameterized PK/PD models. Remifentanil was assumed to be given to the simulated patients, constituting a disturbance to the controller (Fig. 2). A database of 500 cases was hence generated considering the synergistic nonlinear interaction between propofol and remifentanil in the DoA (Table 1).

Weight, height and age covariates needed to calculate the parameters in the PK models were randomly generated following a uniform distribution, considering weight \( \in [60, 80] \) kg, height \( \in [160, 180] \) cm, and age \( \in [18, 70] \) years.

The reference DoA was set at 50 after induction (Fig. 2). Zero-mean measurement noise with variance 9 was added to the system output.
4.2 Controller performance analysis

For each simulated case \( i, \{i = 1, ..., 500\} \), the overall performance of the closed-loop system was characterized on the basis of the performance error [19]

\[
P E_i(kh) = \frac{y(kh) - y^{ref}(kh)}{y^{ref}(kh)} \times 100.
\]  

(15)

The median performance error

\[
MDPE_i = \text{Median}\{PE_i(kh), k = 1, ..., N\},
\]  

(16)

where \( N \) is the total number of samples in each case, reflects whether the controlled outputs are systematically either above or below the reference value. The median absolute performance error

\[
MAPE_i = \text{Median}\{|PE_i(kh)|, k = 1, ..., N\},
\]  

(17)

measures the inaccuracy of the controller.

5 RESULTS AND DISCUSSION

The upper plot of Fig. 3a shows the controlled output for all 500 cases in the database. Overall, the tracking performance is good. When remifentanil changes in amplitude (around minutes 85 and 170), the system is able to steer the output back to the reference level of 50. The induction period (initial transient) is short, as required in the clinical practice, with an overshoot of small amplitude in the majority of the cases. It should be noted that the

<table>
<thead>
<tr>
<th>Propofol PK</th>
<th>Remifentanil PK</th>
<th>PD interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>125 male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>125 female</td>
<td>Schneider model [17]</td>
<td></td>
</tr>
<tr>
<td>105 male</td>
<td></td>
<td></td>
</tr>
</tbody>
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Table 1: Database of 500 hundred simulated patients.
output dropped to values around 25 in only 4 of the 500 cases. Since the intubation is considered as a strong stimulus for the patient under surgery and it occurs right after the initial drop in the DoA level, a deeper anesthetic state is recommended during this time to avoid recall of such events and reduce the probability of the presence of pain. The existence of an initial overshoot is, in this sense, actually desirable. The calculated control actions \( u_\text{p} \) (propofol rates) are shown in the bottom plot of Fig. 3a, with an averaged value between 2 and 4 mg/kg/h in steady state. These values are in accordance with the propofol dosage guidelines for maintenance of general anesthesia [20, 21] when used concurrently with remifentanil. Parameter estimates for each case are shown in Fig. 3c. The high spread of the estimates and the presence of outliers, specially clear in the estimates of \( \zeta \) (bottom plot of Fig. 3c), support the need of adaptive control in this application. Results from a representative case are shown in Fig. 3b and 3d.

The MDPE plot in Fig. 4 shows that there is an average negative bias of 0.06% in the reference tracking. As described by the MAPE (bottom plot of Fig. 4), the controller is, on average, 5% inaccurate.

6 CONCLUSIONS

This report presented an adaptive controller for propofol robust to the synergistic effect of remifentanil based on a minimally parameterized SISO Wiener model for the depth of anesthesia. An extended Kalman filter was implemented for online estimation of the continuous-time model parameters. By using the parameter estimates, the Wiener model is exactly linearized at each time step and a linear quadratic Gaussian controller is designed to control the exactly linearized plant online.

With this setup, the main drawback of identifying and controlling an over-parameterized/underexcited model is no more present, as it would be if the standard model describing the anesthetic effect of propofol with ten parameters would be used for the controller design.

The performance and robustness of the controller was assessed by running simulations on a database of 500 patient models considering the synergistic effect of remifentanil as an external disturbance. Good tracking results were obtained, encouraging the implementation of this controller in a clinical environment.

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Figure 3: Results after applying the adaptive controller to all 500 cases in the database: (a) Output (BIS) (upper plot), and propofol rates (bottom plot) for all cases in the database. Mean values are shown in solid black lines; (b) Output (BIS) (upper plot), and propofol rate (bottom plot) for case number 222 in the database; (c) Parameter estimates for all cases in the database; (d) Parameter estimates for case number 222 in the database.

Figure 4: MDPE (upper plot) and MAPE (bottom plot) of all 500 cases in the database.
References


