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ROBUST ADAPTIVE CONTROL OF HYPNOSIS DURING ANESTHESIA

Pascal Grieder[1], Andrea Gentilini[1], Manfred Morari[1], Thomas W. Schnider[2]

[1]ETH Zentrum, Institut für Automatik, Physikstrasse 3, CH-8092 Zürich, Switzerland

[2] Department of Anesthesiology, Inselspital, CH-3010 Bern, Switzerland

Abstract

A closed-loop controller for hypnosis was designed and validated on humans at our laboratory. The controller aims at regulating the Bispectral Index (BIS) - a surrogate measure of hypnosis derived from the electroencephalogram of the patient - with the volatile anesthetic isoflurane administered with a closed-circuit breathing system. The control algorithm consists of a cascaded Internal Model Controller (IMC) where the master loop aims at regulating BIS. The slave loop tracks endtidal concentration references provided by the master controller. In this paper, a new tuning method is presented. First, a robust design procedure which guarantees stability of the slave controller despite parametric uncertainties is described. Then, we will demonstrate how the estimation of the drug's equilibration constant k_{e0} greatly improves performance if the estimated value is used to update the models in the control scheme. In order to do so, an identification scheme for k_{e0} is proposed, which requires estimation of the drug's time to peak effect t_{peak}. The identification algorithm requires few modeling assumptions and guarantees convergence. Simulation results are presented, which quantify both the performance of the identification scheme and the improvement of the closed-loop control performance.

Keywords : **Closed-Loop Control, Internal Model Control (IMC), Hypnosis, Isoflurane, Identification.**

1 Introduction

Closed-loop control in anesthesia is receiving increasing attention both from a research and a clinical perspective [3, 2]. A necessary condition for the feasibility of a closed-loop drug administration scheme is the availability of a measurement for the clinical endpoint to be targeted. Bispectral Index (BIS) monitors provide anesthesiologists with an ideal target for the administration of hypnotic drugs and enable closed-loop hypnotic administration [6].

In general, large model variability severely limits the controller's performance. In order to guarantee stable controller behaviour for the whole population of patients, closed-loop controllers must often be 'detuned'. That is, they are tailored to the worst case situation and consequently tend to be sluggish for the average subject in the population. A possible way to improve performance consists in estimating the particular subject's characteristics during anesthesia. However, on-line adaptation is limited by restricted bandwidth on the inputs to be applied and ethical constraints.

We developed a method for controller design that combines robust and adaptive controller tuning. The design procedure was applied to an existing cascaded Internal Model Controller (IMC) which regulates BIS with isoflurane. A robust design method is used to adjust the aggressiveness of the slave controller to cope with uncertainties in the actuator and in the pharmacokinetic (PK) model. In the pharmacodynamic (PD) model, an identification algorithm which uses the data gathered during the initial uptake of the volatile agent is used to adapt to the specific patient's characteristics. The proposed scheme allows us to identify the equilibration constant of isoflurane without special or additional administration of anesthetic.

After a brief outline of the cascaded IMC controller, the mathematical background of the identification procedure is discussed. Simulation examples are reported, which quantify the accuracy of the estimation algorithm. Then, tuning of the slave and master controller on the basis of the identified equilibration constant are presented. Simulations of the closed-loop controller response are shown, which demonstrate performance improvements.

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Abstract

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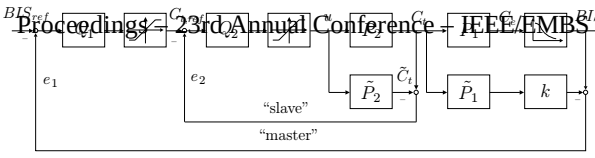

Figure 1: Block diagram of the cascaded Internal Model Control (IMC) to regulate BIS.

2 BIS Controller

A. Controller Setup

In this section the principles of the closed-loop controller are presented. Figure 1 depicts the block diagram of the cascade closed-loop controller to regulate BIS [4]. C_t and $C_{t,ref}$ denote endtidal concentration measurements and references measured as volume percentages. The input of the control system u is the isoflurane concentration in the fresh gas mixture entering the breathing system. u is constrained between 0% and 5% and will be denoted as 'vaporizer setting' from here on. The slave controller Q_2 tracks endtidal concentration references values $C_{t,ref}$ provided by the master controller. The saturation after Q_1 constrains endtidal concentration references between a lower and an upper limit specified by the anesthesiologist. This is done to guarantee minimum delivery of hypnotics and to prevent overdosing, respectively. In Fig. 1, P_2 and $\tilde{P}_2$ represent the transfer functions from the vaporizer setting u to endtidal concentration C_t in the patient and in the parallel IMC model, respectively. The models combine the dynamic description of the closed-circuit breathing system with the PK model of isoflurane.
P_1 and $\tilde{P}_1$ in Fig.1 represent the dynamic model which links endtidal concentration C_t to effect site concentrations C_e [%]. Precisely, we adopted the following first order model:

$$\frac{dC_e}{dt} = k_{e0}(C_t - C_e) \tag{1}$$

where k_{e0} is the equilibration constant at the effect site. Q_2 and Q_1 were chosen as the filtered inverses of the nominal plants [5]. The IMC filters were chosen as:

$$F_i(s) = \frac{1}{(\lambda_i\, s + 1)^{n_i}} \tag{2}$$

with $n_2 = 3$ and $n_1 = 2$ to guarantee strict properness of the controllers. λ_1 and λ_2 affect the speed of the master and slave controller, respectively. More precisely, for a single linear IMC control system with $P = \tilde{P}$, the closed-loop transfer function from reference to output values is $F(s)$ [5].
Among others, one particular advantage of the proposed IMC strategy was exploited in the tuning procedure presented here. Namely, every additional information about the patient or the actuator can be embedded directly into the controller scheme by updating the corresponding parameters in the parallel models. This last aspect is exploited in the proposed adaptive design procedure.

B. Motivating Example

To guarantee controller stability in spite of model uncertainty, the tuning parameters λ_1 and λ_2 were set to relatively high values during initial clinical studies. This in turn decreased the controller's performance for the average subject in our models. Figure 2 illustrates an oscillating closed-loop step response with λ_1 and λ_2 set to 0.6 [min] and 0.4 [min], respectively. In the depicted simulation, parametric uncertainties were considered in the slave control loop. As for the master control loop, we chose $k_{e0} > \tilde{k}_{e0}$. The simulation example suggests that in order to not only improve control performance but also guarantee acceptable controller behaviour, relevant patient characteristics must be identified and used during controller tuning. Among the relevant parameters to be identified, the drug equilibration constant k_{e0} plays a key role. Parametric uncertainties in the slave model on the other hand, have little impact on controller behaviour, since the parameters having the most significant effect on the performance of the slave controller are the parameters of the breathing system. These are modified by the anesthesiologist during surgery and are periodically used to update the paralell model in the slave loop.

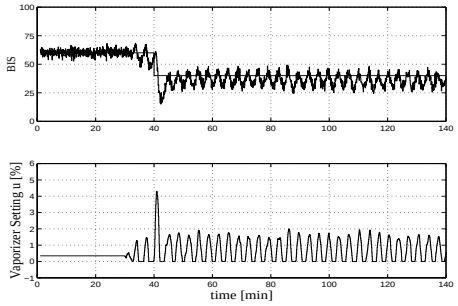

Figure 2: Simulated closed-loop step response with model uncertainty in the slave model. For simulation purposes we set $k_{e0} = 1$ [min^{-1}] and $\tilde{k}_{e0}$ =0.385 [min^{-1}] in the master loop.

3 Mathematical Background

The identification algorithm requires knowledge of the time to peak effect t_{peak} in the BIS profile following a square input of isoflurane. Due to the noise characteristics of the BIS signal, t_{peak} must

bpeak is then used to compute the equilibration constant k_{e0}.

A. Estimation Algorithm

The PD model relating the effect site concentration C_e to BIS is monotone decreasing. Therefore the time to peak t_{peak} of the resulting BIS profile corresponds to the time to peak of the effect site concentration. From (1) we deduce that $C_t(t_{peak}) = C_e(t_{peak})$ where C_t [%] denotes endtidal concentration measurements. In the literature [7] the function

$$F(t, k_{e0}) = C_t(t) - C_e(t, k_{e0}) \tag{3}$$

was considered, for which the patient's equilibration constant k^*_{e0} is such that $F(t_{peak}, k^*_{e0}) = 0$.
To solve (3) for k^*_{e0} a bisection method was proposed [7]. However, since the endtidal concentration measurements do not depend on effect site concentrations, we have:

$$\frac{\partial F}{\partial k_{e0}} \mid_{t=t_{peak}} = -\frac{\partial C_e}{\partial k_{e0}} \mid_{t=t_{peak}} < 0 \quad \forall \quad k_{e0} < k^*_{e0}. \tag{4}$$

To verify the last inequality, note that from (1), the locus $C_t(t)$ can be regarded as the envelope of the maxima of $C_e(t)$ for different values of k_{e0}. This implies that, below $C_t(t)$, $C_e(t)$ is monotone increasing. In particular, the effect site concentration grows faster for higher equilibration constants k_{e0}. Equation (4) allows us to use the Newton algorithm to find the solution k^*_{e0} . The algorithm is iterative and guarantees convergence to the solution at a quadratic rate [1]. According to (4) the initial guess to start the iteration must be smaller than the solution k^*_{e0} (e.g. $k^0_{e0} = 0$). We have:

$$F(0) = C_p(t_{peak}) \tag{5}$$

$$k^{k+1}_{e0} = k^k_{e0} - \frac{F(k^k_{e0})}{F'(k^k_{e0})} \tag{6}$$

In the preceding equations the notation was simplified in the sense that $F(k_{e0})$ stands for $F(k_{e0}, t_{peak})$, as it will be assumed from now on. Endtidal concentrations and BIS are obtained at a sampling time of ΔT= 5 [s]. The discrete equivalent of (1) is:

$$C_e(k+1) = e^{-k_{e0}\Delta T} C_e(k) + (1 - e^{-k_{e0}\Delta T}) C_t(k) \tag{7}$$

where k denotes the generic sampling time. Assuming that the sampling time n_{peak} at which the BIS peak occurs is known, k_{e0} can be computed using the iterative method in (6).

B. Estimation Accuracy

Figure 3 depicts the accuracy of the identification algorithm for the estimated $\hat{k}_{e0}$ as a function of the real k_{e0} and of the measurement noise in BIS. In each plot, 100 simulations were performed for every k_{e0}, assuming that BIS measurements are corrupted by gaussian noise. We excluded equilibration constants such that $k_{e0} > 1[\text{min}^{-1}]$, since there is no discernible difference in behaviour amongst such patients. During the simulation, the vaporizer setting was set to 5% until BIS measurements reached 50. Subsequently, the vaporizer was set to 0% until a minimum was recognizable from the data series. Then automatic control was switched on to maintain a reference BIS of 50. The variance $\hat{\sigma}_{k_{e0}}$ of $\hat{k}_{e0}$ increases with k_{e0}, as can be seen by the boxplots in Fig. 3. This trend can be explained when considering the time profile of both endtidal concentrations and BIS values. In fact, for increasing k_{e0}, t_{peak} converges to the time to peak of the endtidal concentration profile. In these cases we cannot provide an accurate estimate $\hat{k}_{e0}$ from the t_{peak} information. However, for cases with $k_{e0} \leq 1[\text{min}^{-1}]$, when considering the coefficient of variation $CV = \sigma/\mu$, the estimation accuracy is approximately $CV = 0.03$ and $CV = 0.02$ for $\sigma_{BIS} = 4$ and $\sigma_{BIS} = 2.6$ as measurement noises, respectively.

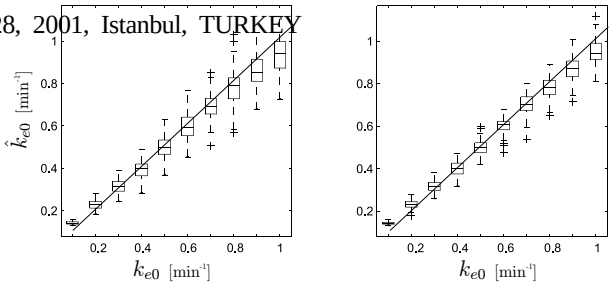

Figure 3: Estimation accuracy of the k_{e0} identification algorithm. Each boxplot depicts the summary statistics of 100 simulations which were performed for every k_{e0}. We assumed that BIS measurements were corrupted by zero mean gaussian noise with variance σ_{BIS}. We adopted $\sigma_{BIS} = 4$ and $\sigma_{BIS} = 2.6$ in the left and right plot, respectively.

4 Controller Tuning

This section will highlight the two fundamentally different approaches for controller tuning in the slave- and the master-loop.
A robust tuning procedure was applied to the slave loop, where a sufficient condition for stability is

$$|F_2(j\omega)| < \frac{1}{l_m(\omega)} \tag{8}$$

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represents an upper bound for the multiplicative uncertainty [5]. We considered variations in both PK and closed-circuit respiratory system parameters such that 85% of the statistical variation around their nominal value is captured. This allows us to use $\lambda_2 = 0.1$ [min] as a lower boundary. In the final implementation we used a $\lambda_2 = 0.4$ in order to gain a safety margin towards general model uncertainty.

Analogously to (8) for the slave controller, plant-model mismatches also limit the aggressiveness of the master controller by imposing a lower bound on λ_1. However, the dynamics of the parallel model in the master controller are exclusively determined by k_{e0}. Consequently, if the estimated k_{e0} is used to update the model in the master controller, we are allowed to decrease λ_1 by virtue of a reduced model uncertainty.

Since there is no established analytical way to analyze a cascaded IMC controller with model uncertainties and non-linear elements, we had to rely on comprehensive simulation to find optimal settings for the filter parameter λ_1. The simulations performed revealed that a $\lambda_1 = 0.6$ [min] suits our specifications best.

5 Controller Performance

The modifications discussed in the previous section guarantee robust control as well as fast settling times even for large model uncertainties, as depicted in Fig. 4, where the modified controller is applied to the worst case scenario introduced beforehand in Fig. 2. Even though the sufficient conditions for robustness allow us deviations in the average subject parameters up to 1.55σ, extensive simulations have shown stable behaviour for parametric uncertainties up to 2σ, which corresponds to more than 95% of the statistical spread of parameters. Unfortunately,

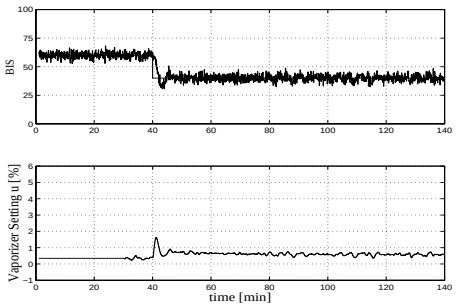

Figure 4: Step response for a model uncertainty of $2\sigma_{BIS}$ with $k_{e0} = 1$ [min^{-1}] and $\tilde{k}_{e0} = 1.3$[min^{-1}]

we were unable to test our tuning algorithm in a clinical environment and are therefore restricted to simulation results.

6 Conclusion

In this paper we presented an approach which aims at improving controller performance in spite of large model uncertainties.

Apart from the improved control performance, we showed that the influence of uncertainties in other PK parameters becomes negligible once the patient's k_{e0} is embedded in the model used for control.

Our tuning approach has decreased average settling times by 35% without generating large overshoots. From the results presented in the paper, one may venture to conclude that the identification of the patient's characteristics is imperative to guarantee an adequate closed-loop performance. Model-based control approaches allow a transparent reconfiguration of the control algorithm on the basis of the identified patient's parameters. Consequently, they emerge as the ideal control strategy for biomedical systems.

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