Predictive Adaptive Control of the Bispectral Index of the EEG (BIS) – Using the Intravenous Anaesthetic Drug Propofol

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Abstract. The problem of controlling the level of unconsciousness measured by the Bispectral Index of the EEG (BIS) of patients under anaesthesia, is considered. It is assumed that the manipulated variable is the infusion rate of the hypnotic drug propofol, while the drug remifentanil is also administered for analgesia. Since these two drugs interact, the administration rate of remifentanil is considered as an accessible disturbance. In order to tackle the high uncertain present on the system, the predictive adaptive controller MUSMAR is used. The performance of the controller is illustrated by means of simulation with 45 patient individual adjusted models, which incorporate the effect of the drugs interaction on BIS. This controller structure proved to be robust to the remifentanil disturbance, different reference values and noise. A reduction of propofol consumption was also observed when comparing to the real clinical dose used for a similar BIS trend.

1 Introduction

Anaesthesia can be defined as the lack of response and recall to noxious stimuli, involving the use of three drugs, a muscle relaxant, an anaesthetic (hypnotic) and an analgesic. The bispectral index of the EEG (BIS) is a numerical processed, clinically-validated EEG parameter, used as an indicator of the level of hypnosis, measuring the degree of depression in the central nervous system. The BIS is a number between 0 and 100, where values near 100 represent an "awake" clinical state while 0 denotes the maximal EEG effect possible (i.e., an isoelectric EEG). In a surgery, the level of hypnosis should be driven to a value between 40-60 in a few $(3 \sim 5)$ minutes, and kept there.

Overall, general anaesthesia consists of both loss of consciousness through the action of anaesthetic drugs, and the inhibition of noxious stimuli reaching the brain through the acting of the analgesics. The analgesic drug is of great importance since it affects the pharmacodynamics of the anaesthetic drug and

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there is no clear indicator of the degree of pain. The analgesic and anaesthetic drugs are interconnected, since they interact with each other so as to achieve an adequate level of hypnosis (unconsciousness) and analgesia. It is known that remifentanil (analgesic) and propofol (hypnotic, i.e. anaesthetic) potentiate their effects when applied together. In what concerns control, this means that, if the level of hypnosis is controlled by selecting the dose of propofol (manipulated variable), the dose of remifentanil being administered may be considered as an accessible disturbance and its knowledge may be used to increase the controller's performance. Automatic control is playing an increasing role in biomedical applications in a diversity of fields [1,2]. This paper presents a feasibility study of the control of the BIS (level of hypnosis) exploring the above ideas. A simulation study of the control of BIS taking the dose of propofol as manipulated variable and the dose of remifentanil as an accessible disturbance is presented. In order to tackle the high uncertain present on the system, the predictive adaptive controller MUSMAR [3] is used. Simulations performed on a nonlinear model relating BIS with the doses of propofol and reminfetanil yield results complying with the specifications. The BIS model is presented in section 2, including the pharmacokinetic and pharmacodynamic structure. Section 3 describes the structure of the adaptive controller. Section 4 presents the results of the simulations under different conditions. The conclusions are presented in section 5.

2 Bispectral Index (BIS) Model

The clinical data of 45 neurosurgeries were used in a previous studies [4,5] to test the model structure. The model parameters were adjusted to the individual patients during the first 15 minutes of induction of anaesthesia, and used to predict the BIS signal during surgery. The model results were validated for the 45 cases, using the real propofol and remifentanil doses (ml/h). Figure 1 shows the real propofol and remifentanil doses (ml/h), and BIS signal (filtered with a Butterworth filter of order 2) for Patient 8 as an example. In this case the BIS signal was maintained by the clinician around the level of 40, and the infusion rates of the drugs were changed accordingly. The maximum rate allowed by the syringe pumps is 1200 ml/h. Figure 2 shows the block diagram of the BIS model. The objective is to describe the relationship between the drugs effect concentrations and its effect. The pharmacokinetic/pharmacodynamic (PKD) models of the two drugs use a 3-compartment model structure. For propofol, the PKD parameters from Marsh [6] were used, whereas for remifentanil the parameters from Minto [7] were used. The PKD model for remifentanil has its parameters adjusted to age, gender and lean body mass of the patients, whereas the PKD model for propofol only takes into consideration the patient's weight.

Bruhn et al. [8] used an interaction model to relate the electroencephalographic parameter values (including BIS) to the effect concentrations of propofol ($Ce_p(t)$ $\mu g/ml$) and remifentanil ($Ce_r(t)$ ng/ml) . This model was developed by Minto et al. in a previous study [9]. First, the effect concentrations were normalised to their respective potencies (EC_{50p} and EC_{50r} for propofol and

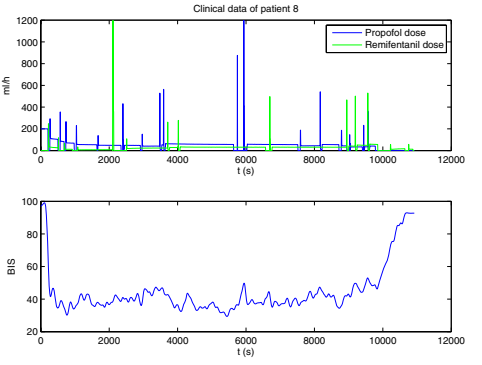

Fig. 1. Real propofol and remifentanil doses (ml/h), and BIS signal (filtered) for the clinical case of Patient 8

remifentanil, respectively), i.e. the effect concentration at half the maximal effect:

$$U_{remi}(t) = \frac{Ce_r(t)}{EC_{50r}} \quad , \quad U_{prop}(t) = \frac{Ce_p(t)}{EC_{50p}} \tag{1}$$

where Ce_r and Ce_p are the respective effect concentrations of remifentanil and propofol. The potency of the drug mixture depending on the ratio of the interacting drugs is modelled as (2).

$$\theta(t) = \frac{U_{prop}(t)}{U_{prop}(t) + U_{remi}(t)} \tag{2}$$

By definition, θ ranges from 0 (remifentanil only) to 1 (propofol only). Thus, the concentration-response relationship for any ratio of the two drugs regardless of the type of interaction can be described as (3).

$$BIS(t) = BIS_0 \left(1 - \frac{\left(\left(U_{prop}(t) + U_{remi}(t) \right) / U_{50(\theta)}(t) \right)^{\gamma}}{1 + \left(\left(U_{prop}(t) + U_{remi}(t) \right) / U_{50(\theta)}(t) \right)^{\gamma}} \right) \tag{3}$$

where BIS_0 is the effect at zero concentrations (e.g. $BIS_0 = 97.7$ for the case of BIS - monitor restriction), γ is the steepness of the concentration-response relation, and $U_{50(\theta)}$ is the number of units (U) associated with 50% of maximum effect at ratio θ. According to [9], (2) can be simplified to a quadratic polynomial (4).

$$U_{50(\theta)}(t) = 1 - \beta_{2,U50}\theta(t) + \beta_{2,U50}\theta^2(t) \tag{4}$$

3 The Adaptive Control Algorithm

The algorithm used is the predictive adaptive controller MUSMAR [3] that aims at minimizing a quadratic cost and reads as follows.

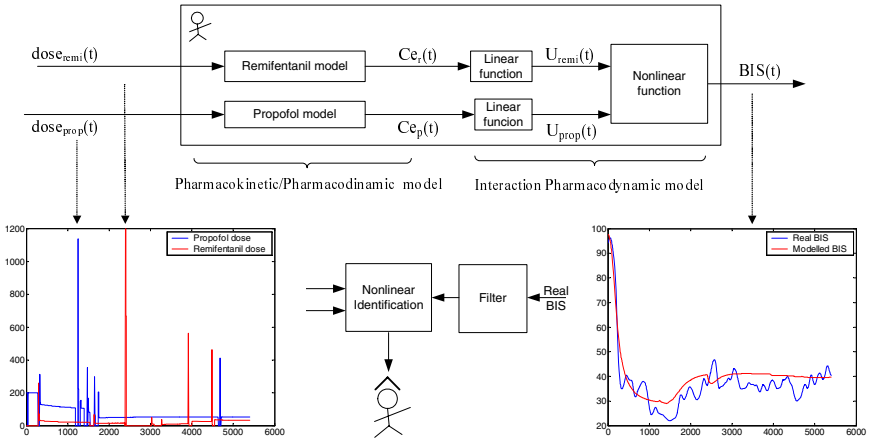

Fig. 2. Block diagram of the Bispectral Index (BIS) model, including the individual pharmacokinetic/pharmacodynamic models for propofol and remifentanil, and the nonlinear interaction model describing the drugs synergistic effect on BIS. The graphs show the remifentanil and propofol doses (on the left) and the real BIS signal versus the modelled BIS (on the right), for patient 23.

At the beginning of each sampling interval t (discrete time), recursively perform the following steps:

1.Sample plant output, $y(t)$ and compute the tracking error $\tilde{y}$, with respect to the desired set-point $ref(t)$, by:

$$\tilde{y}(t) = ref(t) - y(t) \tag{5}$$

2.Using Recursive Least Squares (RLS), update the estimates of the parameters θ_j, ψ_j, μ_{j-1} and ϕ_{j-1} in the following sets of predictive models ($j = 1, \ldots, T$):

$$\tilde{y}(t+j) \approx \theta_j u(t) + \psi_j' s(t) \;\;,\;\; u(t+j-1) \approx \mu_{j-1} u(t) + \phi_{j-1}' s(t) \tag{6}$$

where $\approx$ denotes equality in least squares sense and $s(t)$ is a sufficient statistic for computing the control, hereafter referred to as the pseudo-state, given by

$$\begin{aligned} s(t) = [&\tilde{y}(t) \ldots \tilde{y}(t-n_a+1)\, u(t-1) \ldots u(t-n_b) \\ &ref(t) \ldots ref(t-n_g+1)\, v(t) \ldots v(t-n_v+1)] \end{aligned} \tag{7}$$

with $v(t)$ as the accessible disturbance, and $u(t)$ as the controller output [3]. Since, at time t, $\tilde{y}(t+j)$ and $u(t+j)$ are not available for $j \geq 1$, for the purpose of estimating the parameters, the variables in (6) are delayed in block of T samples.

3.Apply to the plant the control given by

$$u(t) = f' s(t) + \eta(t) \tag{8}$$

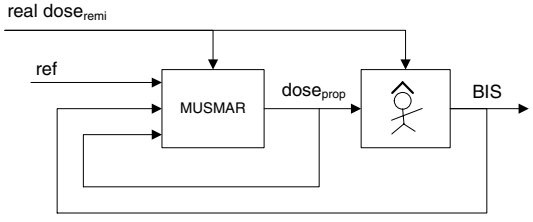

Fig. 3. Block diagram of the control system structure: the dose of remifentanil $dose_{remi}(t)$ is the real dose used for the identified patient (accessible disturbance - $v(t)$), the dose of propofol $dose_{prop}(t)$ is obtained from the MUSMAR controller (controller output - $u(t)$), the Bispectral Index $BIS(t)$ signal is the patient model output (controller input - $y(t)$), and $ref(t)$ is the reference target for BIS.

where η is a white dither noise of small amplitude and f is the vector of controller gains, computed from the estimates of the predictive models by

$$f = -\frac{1}{\alpha}\left(\sum_{j=1}^{T}\theta_j\psi_j + \rho\sum_{j=1}^{T-1}\mu_j\phi_j\right) \quad , \quad \alpha = \sum_{j=1}^{T}\theta_j^2 + \rho\left(1+\sum_{j=1}^{T-1}\mu_j^2\right) \tag{9}$$

where ρ is a positive weight on the control action and α is the normalization factor. The choice of the variables and the number of their past samples entering $s(t)$ defines the structure of the controller. The choice of n_a and n_b should be such that it allows to capture the dominant dynamics of the system. It should be kept in mind that too big values of n_a and n_b imply more parameters to estimate and this may lead to identifiability problems, in turn causing loss of control performance. The pseudo state $s(t)$ includes samples accessible disturbances to embody feedforward action. This will be further discussed below. Figure 3 shows the block diagram of the control system structure used.

4 Results

A number of simulations [10], with a specific patient model (representing patient 23) have been conducted in order to find the best configuration defined by the MUSMAR parameters T, n_a, n_b, n_g and n_v with a sampling interval of $5s$ (the one used for real data collection). This lead to the choice of $T = 5, n_a = 9, n_b = 10, n_g = 1, n_v = 1, \rho = 0.0001, \sigma_\eta = 0.02$. The reasons for these values are presented and analised in [10]. The controller gains obtained using the model of Patient 23 without the disturbance of remifentanil, were used as the initial gains for all the other 44 patient models. But this time, the real remifentanil dose (per patient) was used as the accessible disturbance. The cost function J_k was calculated for each simulation ($k = 1, \ldots, 45$) after the initial $5min$ (10).

$$J_k = \frac{1}{n}\sum_{t=0}^{n}\left((ref(t) - BIS(t))^2 + \rho\, dose_{prop}^2(t)\right) \quad k = 1, \ldots, 45 \tag{10}$$

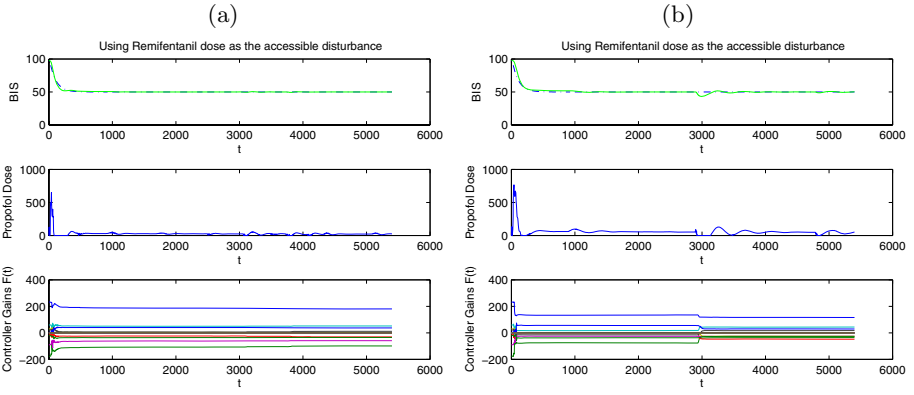

Fig. 4. BIS (model output), propofol dose (ml/h) (controller output), and the MUSMAR controller gains, for a reference BIS target value of 50: (a) using patient model 34 (b) using patient model 11

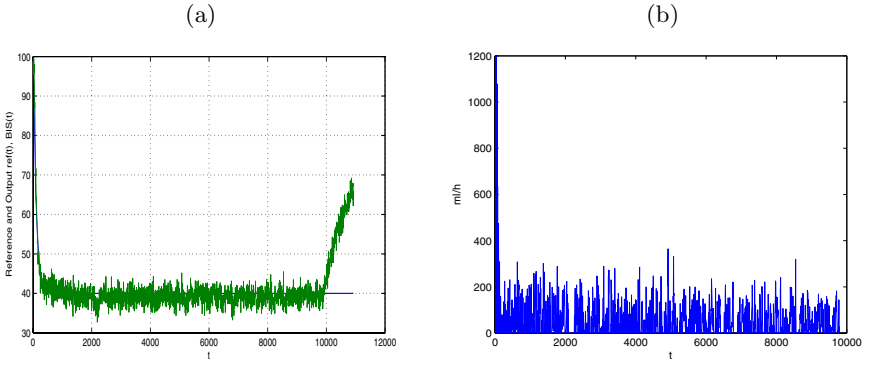

Fig. 5. Simulation using patient model 8 for a reference BIS target value of 40. Gaussian noise (zero mean and variance 3) was added to the model output (BIS) before the feedback to the MUSMAR controller: (a) Bispectral Index (BIS - model output) (b) Propofol dose (ml/h) (controller output).

The minimum and maximum values of J were 0.16 and 2.05 (mean value of 0.66), for patient model 34 and patient model 11, respectively. Figure 4 shows the BIS *versus* target reference, the propofol dose ($dose_{prop}(t)$ -controller output) and the MUSMAR controller gains (9) for the simulations with patient model 34 and 11. The controller is able to follow the BIS reference value of 50 in all simulations, and adequately adjusts its gains to cope with the patient's intervariability and individual remifentanil infusion scheme. In Patient 11 (figure 4 (b)) there was a big remifentanil bolus at around 3000s which made the BIS signal decrease. Nevertheless, the controller is able to respond adequately to such a big disturbance and brings the BIS value back to the reference, adjusting the gains accordingly.

To further evaluate the performance of the MUSMAR controller, the target BIS reference value was changed so as to compared with similar BIS level in the individual clinical cases. In addition, gaussian noise (zero mean and variance 3) was added to the model output (BIS) before the feedback to the MUSMAR controller. Figure 5 shows the BIS signal for the simulation with patient model 8, considering a reference value of 40. Comparing figure 5 with figure 1, the BIS level is very similar. Figure 5 also shows the propofol dose (controller output) for the same simulation with patient model 8. The controller gains were initialised in the same way as the previous simulations, i.e. with the values adapted for patient model 23 without any disturbance. The real remifentanil dose of Patient 8 (figure 1) was used as the accessible disturbance.

The total amount of propofol used in the surgery of Patient 8 was $153.02ml$, while the total amount of propofol used in the simulation was $146.41ml$ to reach a similar BIS value.

5 Conclusions

This control structure (MUSMAR) proved to be efficient to control the BIS value using the dose of the anaesthetic propofol, in extensive simulations using individual patient models adjusted to real clinical data. The fact that the controller gains can be initialised successfully using a specific patient model, with no over/undershoot about the reference value, and adapt to the individual patient intervariability and remifentanil dose (disturbance), shows the robustness of the overall structure. The controller responds to the remifentanil interference and is able to control the BIS value effectively, allowing for the effect of the synergistic interaction between the two drugs. The control structure was also robust to the addition of noise in the BIS signal. This is an important aspect, since in the real clinical data setup noise is present in all signals and a robust controller is necessary. Although the gains were initialised with values adjusted to a specific patient with a reference value of 50, the controller adjusted well to a different reference value and different patients. In the simulation with patient model 8, there was a reduction of $6.61ml$ (4.3%) in the total amount of propofol used, when comparing with the real amount used for that patient during surgery.

These results show that such a control structure could be adequate to control the BIS signal, during total intravenous anaesthesia with a combination of two drugs. It is important, not just that the patient model incorporates the remifentanil effect, but also that the controller is robust to such interaction and changes the propofol dose accordingly. Future work, should show the performance of the controller with dynamic changes in the reference level. Furthermore, for a clinical implementation of the controller an empirical system needs to be incorporated, so as to supervise the online adaptation of the parameters.

A key feature in the control of anaesthesia is to achieve a good rejection of disturbances caused by interfering actions from various sources. The practitioner knows what the surgeon is doing, as well as his own actions, and is therefore able to anticipate the corresponding induced disturbances, acting to counteract

them even before their effects are visible. A major challenge for the automation of anaesthesia consists in replicating similar performances. Clearly, this calls for the use of feedforward from measurable signals correlated with disturbances. The use of predictive control laws is also an immediate suggestion in this respect.

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