Predictive Adaptive Control of Unconsciousness – Exploiting Remifentanil as an Accessible Disturbance

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Abstract—The problem of controlling the level of unconsciousness measured by the BIS index of patients under anesthesia, is considered. It is assumed that the manipulated variable is the administration rate of propofol, while remifentanil is also administered for analgesia. Since these two drugs interact, the administration rate of remifentanil is considered as an accessible disturbance. A predictive adaptive controller structure that explores this fact is proposed and illustrated by means of simulation.

I. INTRODUCTION

Automatic control is playing an increasing role in biomedical applications in a diversity of fields, ranging from the optimization of therapeutics in cancer [1] and in immunology (e.g. HIV 1 infection [2]) and complex biochemical processes [3], to anesthesia [4], [5], not to mention the wide field of prosthetics construction and artificial organs. The systems view upon which control relies provides an adequate framework to understand the complex dynamic phenomena underlying life, at least as long as the substrate to engineering design of ancillary systems is concern. In this respect, it is worth to mention that, as discussed in [6], all the major groups performing research in the therapy of HIV infection work in association with a group of mathematicians.

General anesthesia of patients undergoing surgery – the example of concern in this paper – consists in a sequence of clinical procedures to induce an adequate physiological state, and comprises three main components:

- Areflexia;
- Analgesia
- Hypnosis

Areflexia (lack of movement) aims at driving the body to an adequate level of paralysis, measured by an index between 0 (“full paralysis”) and 100 (“normal” state), and is induced by drugs causing neuromuscular blockade. It is prone to the use of automatic control techniques by closing the loop with a suitable sensor and a computer controlled syringe. See [7] and the references there listed.

Analgesia prevents pain and the phenomena associated to it, e.g. the increase of heart rate. It is achieved through the administration of opioid drugs such as remifentanil. There is no direct sensor providing a unique index of the level of analgesia. Instead, the patient’s state is inferred by the practitioner from the observation of related measurements, such as the EEG, and of the cardiovascular functions.

Hypnosis is defined by the degree of unconsciousness, a variable for which there are several sensors that provide an index between 0% (deepest level of hypnosis) and 100% (“full awake” state). Available sensors include evoked auditory potentials, a measure of the complexity of the EEG and the bispectrum of the EEG (BIS index). In surgery, the level of hypnosis should be driven to a value between 45% and 60% in a few (3 ~ 5) minutes, and kept there. Higher values correspond to an insufficient loss of consciousness. There is clinical evidence that a peak of the hypnosis index, staying above 60% only for a few seconds, corresponds to a suffering/stress state of the patient. Values below 45% are also undesirable since they can apparently be correlated with complications in the post-operatorium and with an increase of the death rate after one year.

A common method of administration of hypnotic drugs consists in gas inhalation. However, the use of intravenous administration of drugs such as propofol leads to the same hypnotic effect with a smaller dose. It also provides an actuator suitable for automatic control by using a computer controller dosing syringe.

Anesthesia is a complex process. The drugs employed affect not only the brain but also other organs such as the heart. Furthermore, while the interaction between the drug used for muscle relaxation with the drugs used for the two other functions may be neglected, this is no longer true for the drugs inducing analgesia and hypnosis. Indeed, it is known that propofol (used mainly for analgesia) and remifentanil being administered may be considered as an accessible disturbance and its knowledge may be used to increase the controller’s performance.

A key feature in the control of anesthesia 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 anesthesia 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 [8] is also
an immediate suggestion in this respect.

Since a significant degree of uncertainty on the models representing anesthesia is involved, adaptive control is an-
other natural approach to consider. An early trial, including clinical tests, used model reference adaptive control [9].
Recent work comprises nonlinear techniques [10], [11].

This paper presents a feasibility study of the control of the depth of unconsciousness 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 uncertainty present on the system, the predictive
adaptive controller MUSMAR [12] is used. This algorithm has the advantage of easily allowing the introduction of
feed-forward terms from accessible disturbances without requiring the a priori knowledge of the corresponding data.
Simulations performed on a nonlinear model relating BIS with the doses of propofol and remifentanil yield results
complying with the specifications.

The paper is organized as follows: After this introduction in which the problem to consider is motivated and formu-
lated, the interaction model of propofol and remifentanil is described in section 2. Section 3 describes the control
algorithm employed and the results obtained are presented and discussed in section 4. Conclusions are drawn in section
5.

II. BISPECTRAL INDEX (BIS) MODEL

The clinical data of 45 neurosurgeries were used in a previous study [13], [14] to test the model structure. The model
parameters were adjusted to the individual patients during the first 15 minutes of induction of anesthesia, and used to predict the bispectral index (BIS) signal during surgery. The model results were validated for the 45 cases, using the real propofol and remifentanil doses. However in this study only the model for patient 23 will be used.

Fig. 1 shows the block diagram of the Bispectral Index (BIS) model. The objective is to describe the relationship be-
tween 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 [15] were used, whereas for remifentanil, the parameters from Minto [16] were used. The PKD model for remifentanil has its parameters adjusted to age, gender, weight and height of the patients, whereas
the PKD model for propofol only takes into consideration the patient’s weight.

In [17] an interaction model is used to relate the electroen-
cephalographic parameter values (including BIS) to the effect
concentrations of propofol and remifentanil. This model was
developed in a previous study [18]. First, the concentrations
were normalised to their respective potencies ($EC_{50p}$ e
$EC_{50r}$ for propofol and remifentanil, respectively), i.e. the
effect concentration at half the maximal effect:

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

where $Ce_r$ and $Ce_p$ are the respective effect concentrations of remifentanil and propofol. For an additive interaction, the "effective" concentration is the sum of the individual concentrations normalised. Therefore the effect (in this case the effect is BIS) can be described as

$$BIS(t) = BIS_0 \left( 1 - \frac{U_{prop}(t) + U_{remi}(t)}{1 + U_{prop}(t) + U_{remi}(t)} \right) \quad (2)$$

where $BIS_0$ is the effect at zero concentrations (e.g. $BIS_0 = 97.7$ for the case of BIS - monitor restriction). Deviation from a purely additive interaction is modelled by changing the potency of the drug mixture depending on the ratio of the interacting drugs. This yields

$$\theta(t) = \frac{U_{prop}(t)}{U_{prop}(t) + U_{remi}(t)}. \quad (3)$$

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

$$BIS(t) = BIS_0 \left( 1 - \frac{(U_{prop}(t) + U_{remi}(t)) / U_{50(\theta)}(t) \gamma}{1 + ((U_{prop}(t) + U_{remi}(t)) / U_{50(\theta)}(t) \gamma) \gamma} \right), \quad (4)$$

where $\gamma$ is the steepness of the concentration-response rela-
tion, and $U_{50(\theta)}$ is the number of units ($U$) associated with 50% of maximum effect at ratio $\theta$. According to [18], (3) can be simplified to a quadratic polynomial of the following form:

$$U_{50(\theta)}(t) = 1 - \beta_{2,U50} \theta(t) + \beta_{2,U50} \theta^2(t). \quad (5)$$

III. THE ADAPTIVE CONTROL ALGORITHM

The algorithm used is the predictive adaptive controller
MUSMAR [12] that aims at minimizing a quadratic cost
and reads as follows:

MUSMAR algorithm with feed-forward
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 $\hat{y}$, with respect to the desired set-point $ref(t)$, by:

$$\hat{y}(t) = ref(t) - y(t) \quad (6)$$

2. Using Recursive Least Squares (RLS), update the
estimates of the parameters $\theta_j$, $\psi_j$, $\mu_{j-1}$ and $\phi_{j-1}$ in the
following sets of predictive models:

$$\hat{y}(t + j) \approx \theta_j u(t) + \psi_j s(t) \quad (7)$$

$$u(t + j - 1) \approx \mu_{j-1} u(t) + \phi_{j-1}s(t) \quad (8)$$

$$j = 1, \ldots, T$$
Fig. 1. Block diagram of the BIS model, which includes 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. The modelled BIS signal was obtained through the filtered real BIS signal and the respective drugs doses, using nonlinear identification for the model parameters.

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

\[
s(t) = ([\hat{y}(t)] \ldots \hat{y}(t-n_a+1) u(t-1) \ldots u(t-n_b) \quad \text{ref}(t) \ldots \text{ref}(t-n_g+1) v(t) \ldots v(t-n_v+1))^T, \tag{9}
\]

with \( v(t) \) as the accessible disturbance (either remifentanil dose or remifentanil effect concentration) and \( u(t) \) as the controller output. Since, at time \( t \), \( \hat{y}(t+j) \) and \( u(t+j) \) are not available for \( j \geq 1 \), for the purpose of estimating the parameters, the variables in (7,8) are delayed in block of \( T \) samples.

3. Apply to the plant the control given by

\[
u(t) = f's(t) + \eta(t), \tag{10}\]

where \( \eta \) 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

\[
f = -\frac{1}{\alpha} \left( \sum_{j=1}^{T} \theta_j \psi_j + \rho \sum_{j=1}^{T-1} \mu_j \phi_j \right), \tag{11}\]

where \( \rho \) is a positive weight on the control action and \( \alpha \) is a normalization factor given by

\[
\alpha = \sum_{j=1}^{T} \theta_j^2 + \rho \left( 1 + \sum_{j=1}^{T-1} \mu_j^2 \right). \tag{12}\]

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 large 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. Due to the independent estimation of the predictive models, MUSMAR is able to tackle the situation in which the controller gains are to be tuned in the (local) minimum of a steady state quadratic cost, constrained to the \( a \ priori \) chosen controller structure [12]. The pseudo state \( s(t) \) includes samples accessible disturbances to embody feed-forward action. This will be further discussed below. Fig. 2 includes the block diagram of the control system structure used.

IV. RESULTS

A number of simulations, with different patient models has been conducted in order to find the best configuration...
defined by the MUSMAR parameters $T$, $n_a$, $n_b$, $n_g$, $n_v$, $\rho$ and $\sigma_\eta$ with a sampling interval of 5s (the one used for real data collection). This lead to the choice

- Horizon, $T = 5$
- Number of samples of plant output used for feedback, $n_a = 10$
- Number of samples of plant input used for feedback, $n_b = 9$
- Number of samples of reference to track used in the controller, $n_g = 1$
- Number of samples of the accessible disturbance used in the controller, $n_v = 1$
- Weight of the control penalty in the cost: $\rho = 0.0001$
- Dither noise standard deviation: $\sigma_\eta = 0.02$

Fig. 3 shows the steady state losses obtained with different values of the horizon $T$ for $n_a = 3$ and $n_b = 2$. For very low values of $T$ a large loss is yielded. This due to the fact that the approximation of the steady state (infinite horizon) LWQ controller corresponding to the linearized dynamics seen by the adaptive controller is poor. High values of $T$ also yield an increasing loss, the reason being in this case a decreasing precision of the predictive models. The best values are between 3 and 5. The value $T = 5$ has been selected because it leads to the best results when the orders $n_a$ and $n_b$ are increased.

Since the reference to track and the accessible disturbance are constant for long periods of time, increasing their number of samples in the pseudo-state is useless and leads to identifiability problems that degrade the controller performance.

A. Example 1

The first example compares the performance achieved when using the effect concentration of remifentanil as a feedforward signal of an accessible disturbance (i.e. the last sample of the effect concentration of remifentanil is included in the pseudo-state) with the one yielded by using the dose of remifentanil as feed-forward signal. The results obtained are shown in figs. 4 and 5 for simulations performed without including output noise.

Although the figures seem quite similar, a quantitative analysis shows that using remifentanil dose as a feed-forward signal leads to better results than the use of remifentanil effect concentration. In practical terms, this is an advantage because, while the dose signal is readily available for measure, measuring the effect concentration would be quite difficult.

B. Example 2

This example shows the effect of using *a priori* information from the patient to avoid start-up adaptation transients. Results are shown in figs. 6-11. The first three figures, figs. 6, 7 and 8 show a situation corresponding to example 1,
Fig. 6. Example 2. No a priori information about the controller gains is available. BIS, when the dose of remifentanil [ml/hr] is used as accessible disturbance. Simulation with the patient model 23 with output noise.

Fig. 7. Example 2. No a priori information about the controller gains is available. Propofol dose (MUSMAR output) when the dose of remifentanil [ml/hr] is used as accessible disturbance. Simulation with the patient model 23 with output noise.

Fig. 8. Example 2. No a priori information about the controller gains is available. Controller gains when the dose of remifentanil [ml/hr] is used as accessible disturbance. Simulation with the patient model 23 with no output noise.

Fig. 9. Example 2. Assumes a priori information about the controller gains available to avoid adaptation transient. BIS, when the dose of remifentanil [ml/hr] is used as accessible disturbance. Simulation with the patient model 23 with no output noise.

V. CONCLUSIONS

This paper illustrates by means of simulation, using a model validated with actual patient data, an approach to the control of hypnosis combining the following aspects:

- A predictive adaptive controller is used. This has the advantage of tackling the high levels of uncertainty, together with the delays in the system.
- A feed-forward action from the dose of remifentanil is used (actual clinical results are used as input to the simulation). This has the advantage of being a readily available signal and its inclusion in the controller increases the performance achieved.

The basic type of predictive adaptive control algorithm used (MUSMAR) renders the computation of the feed-
forward term simple and independent of the specific model structure assumed because it relays on direct estimation from plant data.

REFERENCES