ACLAC: An approach for adaptive closed-loop anesthesia control

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Abstract

In current practice, to control the anesthetic process, the anesthetist delivers drugs according to the surgery procedure and to the current patient characteristics and state. This is an open-loop procedure requiring an active participation of the medical expert. We propose an adaptive closed-loop controller for the regulation of hypnosis for patients undergoing general anesthesia. One of the main problems arising when designing such a controller is related to the intra- and inter-patient variability. We employ a simple regression model to make prediction of patient's response and to compute the adequate doses of propofol to keep the patient in the specified Bispectral Index target. To make our model adaptive, we continuously monitor the patient behavior and detect changes in patient response to update the identification model. Experimental evaluation on real patients data shows that we can effectively detect change points. Simulation of the adaptive closed-loop control with the change detection mechanism also suggests that the use of the adaptation mechanism improves the control.

1 Introduction

The main variables appearing in anesthesia are hypnosis, analgesia and muscular relaxation. Hypnosis refers to the level of unconsciousness of the patient. Analgesia is related to the level of insensibility to pain. And muscular relaxation is also a variable of interest to avoid movements during the surgical procedure and to make easier access to patients organs.

In the anesthetic process, the clinician must guarantee an adequate level for these three variables. Traditionally the anesthetist starts with the infusion of the drugs according to well established protocols and then modifies the infusion depending on the patient characteristics and state. As can be observed this is an open-loop procedure.

During last years the introduction of closed-loop methodologies in this field has been a matter of study and some closed-loop strategies have been reported with real patients in the operating theater. These approaches propose to consider both signal-based [10, 15] and model-based control schemes [7, 12]. Most of them are focused in the regulation of the hypnosis level of the patients once they become unconscious. The hypnosis level can be measured through an index extracted from the electroencephalogram (EEG). This variable is called Bispectral Index (BIS) [3] and is well correlated with the level of unconsciousness.

We propose an adaptive closed-loop controller for the regulation of hypnosis for patients undergoing general anesthesia and employ a simple regression model to make prediction of patient's response and to compute the adequate doses of propofol to keep the patient in the specified BIS value target. To make our model adaptive, we continuously monitor the patient behavior and detect changes in patient response to update the identification model.

The rest of the paper is organized as follows. In Section 2 we introduce the problem of anesthesia control and emphasize the challenges to be addressed. In Section 3 we present ACLAC – our approach for adaptive closed-loop anesthesia control that has a change detection mechanism built into it. In Section 4 we discuss the results of the experimental study including the simulation of the closed-loop anesthesia control on the simulated data and the performance of the change detection on the real data collected from ten different patients during in the surgery room. Experimental evaluation on real patients data shows that we can effectively detect change points. Simulation of the adaptive closed-loop control with the change detection mechanism also suggests that the adaptation mechanism is adequate and can be investigated further in the hospital settings. Section 5 concludes with the discussion of the limitation and future work.

2 The problem of anesthesia control

This work focuses on the regulation of hypnosis for patients undergoing general anesthesia. As a feedback vari-

able for a close-loop control of a hypnosis we use the BIS signal. In particular we considered a BIS target of 50 [8, 14]. The hypnotic drug used is intravenous propofol. The control objective is to maintain the BIS in 50 rejecting the disturbances affecting the patient during the procedure: surgical stimuli, blood loss, incisions, etc.

BIS variable is adimensional and varies between 100 (awake state) and 0 (no electrical brain activity). The values between 60 and 40 define the band for general anesthesia.

One of the main problems arising when designing the controller is the patient variability. We can distinguish both inter-patient and intra-patient variability. Inter-patient refers to the variability appearing in the response to the drug between different patients. And intra-patient variability appears because of change in the response during surgery of the same patient along the procedure.

An important specification that the closed-loop controller must satisfy is the robustness to this variability. From the control engineering point of view, two different approaches can be used. The basis of robust control is to design a fixed controller that offers satisfactory performance even if the patient response changes. A different option is the use of adaptive controllers that includes adaptation mechanism to change in response to changes in the patient.

In this work, we propose a predictive adaptive controller that continuously monitors the patient behavior, propose a model to make prediction of his response and computes the adequate doses of propofol to keep the patient in the specified BIS target.

The sample time considered is 5 seconds. Although, according to patient response, a bigger value can be considered, this sample time is large enough to guarantee the applicability of the controller in terms of computational burden.

3 Approach

Our approach consists of three main components: adaptive patient modeling, control and change detection mechanisms that we describe in the corresponding subsections.

3.1 Adaptive modeling of hypnosis

The common approach to model the patient dynamics to propofol infusion is the use of compartmental models. This approach considers different compartments interconnected and with a given time constant. Drug is infused in the main compartment, and from then is transferred to the other compartments until equilibrium is reached between all the compartments. A common approach considers four compartments (central, slow, fast and *effect site*) [16]. The BIS variable can be obtained as a nonlinear function of the concentration in the effect site compartment.

We use a linear approximation to this model using an Autoregressive with exogenous input (ARX) model that computes the input signal at sample instant d as a function of the input and output values at previous time instants. The computation of the model parameters is done online by using a least squares minimization algorithm. Consider the following polynomials:

$$A(z^{-1}) = 1 + a_1 z^{-1} + a_2 z^{-2} + ... + a_{na} z^{-na}$$

$$B(z^{-1}) = b_0 + b_1 z^{-1} + b_2 z^{-2} + ... + b_{nb} z^{-nb}$$

where na is the number of previous *outputs* and nb is the number of previous delayed by n_d *inputs* on which the current output depends and z^{-n} is the *delay operator* which is defined by $z^{-n}x(t) = x(t-n)$. Then, the ARX model for the BIS variable can be expressed as:

$$A(z^{-1})BIS(t) = B(z^{-1})u(t-n_d) + e(t)$$

where $BIS(t)$ is the BIS value at t, $u(t)$ represents the propofol infusion rate in $mg/l/min$, $e(t)$ is the residual error and n_d is the input-output delay. Thus, the model can be expressed as:

$$BIS(t) + a_1 BIS(t-1) + ... + a_{na} BIS(t-na) = b_0 u(t-n_d) + b_1 u(t-n_d-1) + ... + b_{nb} u(t-n_d-n_b) + e(t) \quad (1)$$

The estimation for $na = nb = 4$ and $n_d = 1$ was done using least squares algorithm during simulations. The model will adapt to the specific patient response and to eventual changes in its dynamics. Figure 1 shows the identification scheme used.

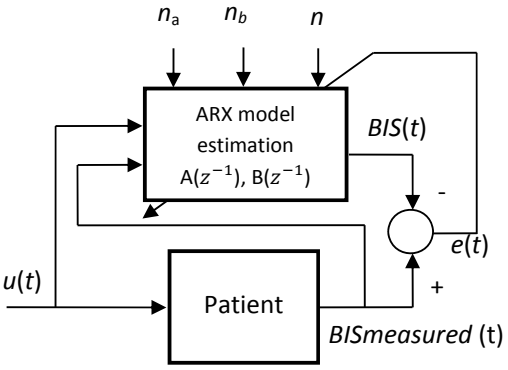

Figure 1. Patient model identification.

The initial model for the patient is estimated from the analysis of a set of real patient data. After the initial training, the adaptation algorithm proposes a new model based on real data of the patient. This model is regularly updated along the time.

The availability of information of patient changes can improve the accuracy of the model identification scheme which would be used to make decisions about the relevance of the patient data used in the algorithm. Thus, one contribution of this paper is the inclusion of a change detection mechanism to detect changes in patient response. In ACLAC we disregard data preceding to a detected change-point. This way, the model update will only include information of the new dynamics of the patient.

3.2 Control approach

The controller proposed to regulate the hypnosis of the patient is shown in Figure 2. The model predictive controller(MPC) decides the adequate profofol infusion rate to be infused to the patient. The MPC uses a linear model for the predictions that is obtained from the model identification module. The change detection algorithm provides information to the identification scheme that is used to determine the time-window of past data used. MPC controller

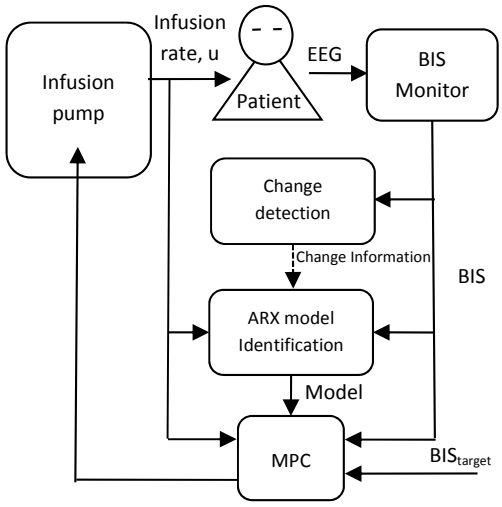

Figure 2. Closed-loop control scheme using identification scheme with change detection.

includes an optimization process in which the best future inputs are computed based on the minimization of a given function costs. The cost function uses predictions obtained with the ARX model.

The formulation of the problem can be done as follows [2]:

$$\min_{u(k|k),\ldots,u(k+p-1|k)} \sum_{i=1}^{p} w_i (BIS(k+i|k) - BIS_{target})^2 + \sum_{i=1}^{c} r_i \Delta u(k+i-1|k)^2 \quad (2)$$

subject to

$$BIS(t) + a_1 BIS(t-1) + \ldots + a_{na} BIS(t-na) = b_0 u(t-n_d) + b_1 u(t-n_d-1) + \ldots + b_{nb} u(t-n_d-n_b) \quad (3)$$

$$BIS_{max} \geq BIS(k+i|k) \geq BIS_{min}, i = 1, \ldots, p$$
$$u_{max} \geq u(k+i-1|k) \geq u_{min}, i = 1, .., c$$
$$\Delta u_{max} \geq \Delta u(k+i-1|k) \geq -\Delta u_{max}, i = 1, .., c \quad (4)$$

where k is the current time instant, p and $c < p$ are the sizes of the prediction horizont and control horizont respectively, BIS_{target} is the target for the BIS, and $u(k+i-1|k)$, $i = 1, \ldots, p$, is the set of future input values, where

$$u(k+i|k) = u(k+c-1|k), i = c, \ldots, p-1$$
$$\Delta u(k+i-1|k) = u(k+i-1|k) - u(k+i-2|k) \quad (5)$$

The optimization problem is solved at time instant k. Under this approach, the control law for $u(k|k)$ is obtained by solving a quadratic programming problem. The optimal input $u(k) = u_{opt}(k|k)$ is applied to the plant. This process is repeated in subsequent times $k+1, k+2$, etc. Thus the new control law $u(k+1|k+1)$ may be different from the control signal calculated above. This principle is called moving horizont strategy.

3.3 Change detection method

The term change point stands for a phenomenon when statistical properties of a data stream change significantly over time. In medical sensor data streams we can observe changes of different types: change in the mean value, variance, autocorrelation, in the seasonal and trend components, etc. Changes can be classified also with respect to the rate of the change into abrupt and gradual changes. These changes, strictly speaking, are happening almost continuously (depending on the 'scales' of the changes which we consider). One of the problems is to define rules by which we can determine whether change is significant and should be detected or not. Such rules can be constructed using state-of-the-art change detection methods based on control charts, cumulative sum (CUSUM, [13]), heuristic (thresholding) approaches, two sliding windows statistic monitoring (w.r.t. data or modeling error), likelihood and density ratio estimation for two competitive models among others [11].

We are interested in detection of the change in the mean value because a BIS target value is 50 and control limits are defined by horizontal lines of values 40 and 60.

In the domain of depth of anesthesia monitoring the problem of change detection has been studied recently [18].

A Page-Hinkley test with a forgetting mechanism (PHT-FM) was proposed in [17]. This method is on-line, but it needs threshold value tuning that maybe not easy to achieve in our case when dealing with noisy data or presence of outliers. Also it requires the availability of training data on which the models can be tuned.

For our purposes we need a method which satisfies the following conditions: 1) it is applicable in an on-line settings, 2) it is able to detect multiple change points, 3) it should take into account all detected change points and decide on-line which of them should be dropped because of the change in the scales of the changes.

The commonly used approach for a single change point in a fixed interval is to perform likelihood ratio test. In case of a single change point the null hypothesis H_0 is no change point, alternative hypothesis H_1 is a single change point at the moment of time τ. In other words, likelihood ratio test compares the fit of two models, one of which is a special case of the other. Given sequence of data $y_{1:n} = (y_1, ..., y_n)$, it is said that change point occurs at the moment of time τ, such that the statistical properties of $(y_1, ..., y_\tau)$ and $(y_{\tau+1}, ..., y_n)$ are different accordingly to the chosen rules. Twice the negative log-likelihood ratio function is used as a test statistic to decide whether the change has occurred.

$$L(\tau) = \sum_{i=1}^{\tau} \log p(y_i|\hat{\theta}_0) + \sum_{i=\tau+1}^{n} \log p(y_i|\hat{\theta}_1) \qquad (6)$$

where $\hat{\theta} = (\mu, \sigma)$ is the maximum likelihood estimate of the parameters from likelihood function:

$$\log p(y_{1:n}|\theta) = -\frac{n}{2}\log(2\pi) - \frac{n}{2}\log(\sigma^2) - \frac{1}{2\sigma^2}\sum_{i=1}^{n}(y_i - \mu)^2$$

The test statistic is

$$\gamma = C(y_{1:n}) = 2[\max_{\tau} L(\tau) - \sum_{i=1}^{n} \log p(y_i|\hat{\theta})] \qquad (7)$$

where $\max_{\tau_1} L(\tau)$ is the maximum log-likelihood value under the alternative hypothesis. The null hypothesis is rejected if $\lambda > c$ where c is selected threshold.

In case of multiple change points the following function should be minimised:

$$\sum_{i=1}^{m+1} [C(y_{(\tau_{i-1}+1):\tau_i})] + \beta \qquad (8)$$

where m is the number of change points, C is the twice negative log likelihood cost function(Eq. 7) and β is a penalty term [6] to prevent overfitting. Value of β was tuned during experiments. The combination of on-line monitoring algorithms and time-series segmentation methods is a promising approach for BIS monitoring because we often do not know in advance scales of the changes. Therefore, we have to perform analysis offline over detected points in order to discard (or keep) some of them if it is necessary. For multiple change points detection we use PELT method [6], which is based on dynamic programming optimal partitioning algorithm proposed in [4]. Optimal partitioning algorithm performs recursive process that minimise function(Eq. 8). PELT method contains the pruning step within the dynamic program which reduces computational cost of the method. Comprehensive overview of the methods and description of the optimal partitioning and PELT algorithms with pseudo-codes can be found in [6, 5].

4 Experimental study

The validation of the proposed algorithm is done using real data obtained from 10 patients undergoing general anesthesia. Patients are non premedicated of ASA class I-II, scheduled for gynecological or abdominal surgery with an estimated duration more than 30 minutes. A laptop PC records both the BIS values and the infusion rate using RS-232 links. The measurement of the BIS variable is done with a BIS-XP™ monitor (Aspect Medical System) connected using a RS-232 link and using four $ZipPrep$® electrodes. A Graseby 3500® infusion pump (Graseby Medical Ltd) with propofol 1% is the actuation system and was also connected via RS232 port to the PC. Sample time was 5 seconds. The data collected included both the induction and the maintenance phase. In the induction phase a bolus dose is applied to take the patient rapidly to the target area. In the maintenance phase the infusion rate is calculated to keep the patient in the target BIS.

4.1 Evaluation of change detection

Change points for two signals are shown in Figures 3 and 4 (vertical dashed red lines). The horizontal lines depict the target value and the general anesthesia band. In Figure 3 we can see that the detected change points divide observations into four stages. The first stage is short and has a high variance, but BIS is the in control limits. In the second stage BIS is between the target value and the upper limit. In the third stage BIS is below the target value, but above the lower limit. In the fourth stage BIS is fluctuating around the target value. In Figure 3 we can see that all out of limits periods are detected by the change detection mechanism.

The detected change points represent 'changes' in a statistical sense. It is described in subsection 3.3. Visual inspection of changes is difficult even for the domain experts. Having no exact points on the BIS signals denoting ground

truth changes makes its hard to assess accuracy of detection in a quantitative way.

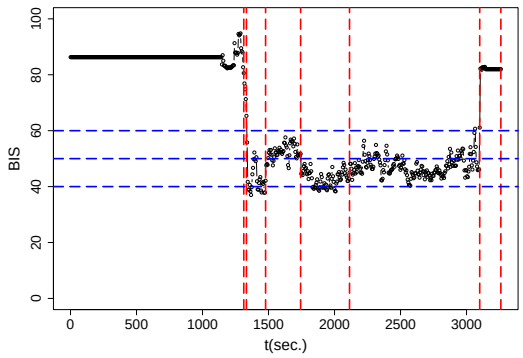

Figure 3. Four stages detected in BIS.

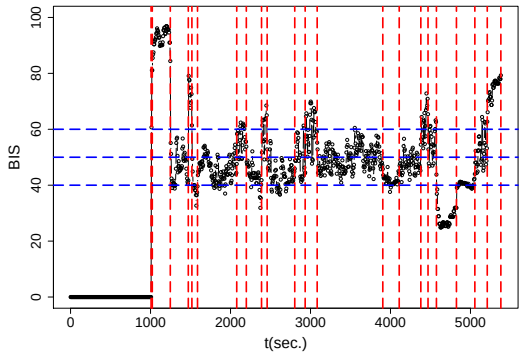

Figure 4. Case of BIS with high variance.

4.2 Closed-loop control evaluation

The evaluation of the proposed controller Fig. 2) was done in simulation of the patient response using the Schnider compartmental model [16] for one standard patient(male, 70Kg, 175cm).

BIS target is 50 and sample time is 5 seconds. In the simulations performed we replicate the procedure of the anesthetist. First a bolus dose of $2mg/kg$ is infused at maximum infusion rate and, after this, the automatic mode starts.

Figure 5 shows the results obtained with ACLAC. Two disturbances are considered in the patient dynamics in $t = 20.8$ *min* and $t = 33.3$ *min*. The origin of these disturbances can be surgical stimulus, blood loss, etc. The result is a change in the patient state and in the patient model parameters. Before these disturbances occur the controller is able to regulate the state of the patient to 50. In the figure, the model predictions are depicted in dotted line. As can be observed the prediction errors are low. When the disturbance occurs, the change detection algorithm detects a change in the patient behavior and this information is used in the identification scheme to improve the identification. The identification module does not update to a new model until it have data enough to guarantee correct model identification. Thus, after the first disturbances arrives, the model update is done again at $t = 26.4$ *min*.

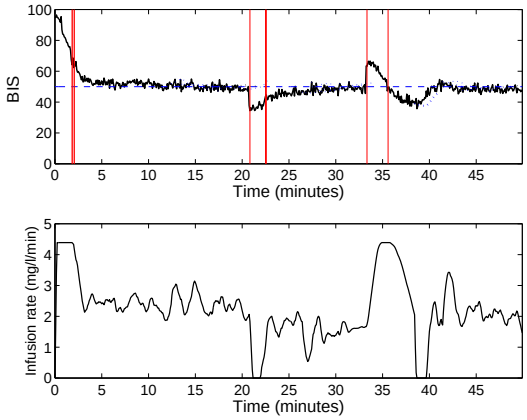

Figure 5. ACLAC simulation result. Disturbances appears at $t = 20.8$ min and $t = 33.3$ min. The upper figure shows BIS evolution (solid line), BIS target (dashed line) and model predictions (dotted line). Vertical lines indicate detected change points. The lower figure presents the infusion rate.

Figure 6 shows a comparison of the proposed ACLAC performance is done with a similar algorithm without change detection. Change detection is shown with vertical lines. We can see that if there are no disturbance both approaches show identical performance. However, after the disturbance affects the patient, ACLAC (solid line) performs better than a similar controller without an explicit change detection mechanism. The disturbance rejection is quite effective with ACLAC. Observe that the algorithm without change detection is not able to take the patient quickly to the target due to the use of a less accurate model.

5 Conclusion and future work

Close-loop control of hypnosis for patients undergoing general anesthesia is an important problem that is challenging because of the inter- and intra-patient variability in response behavior. We proposed ACLAC - an adaptive scheme of the controller that uses explicit change detection mechanism for quicker adaptation to the changes in patients response.

We performed experimental evaluation of the change detection mechanism on real data collected from the patients

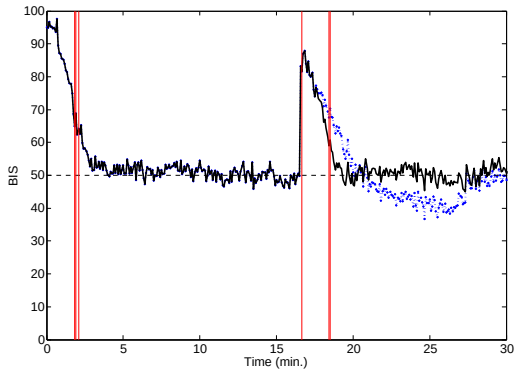

Figure 6. Comparison of ACLAC (solid line) and predictive controller using a fixed time window for identification (dotted line) instead of relying on explicit change detection.

and of ACLAC as a whole in the simulation. The results indicate that introduced explicit change detection mechanism indeed improves the performance of ACLAC in comparison with analogous adaptive schemes based on fixed time window instead of detecting changes.

In our future work we plan to (1) perform more extensive evaluation of the considered change detection method with other relevant approaches including e.g. PHT-FM [17], CUSUM [13], ADWIN [1] and Quantile Index [9] on a larger set of BIS signals, and (2) validating the proposed closed-loop hypnosis control approach in the real operational settings, i.e. in a surgery room.

Acknowledgements. This work is under the auspicious of the research Project DPI2010-18278 supported by "Ministerio de Ciencia e Innovacin" of the Spanish Government.

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