Robust Predictive Control Strategy Applied for Propofol Dosing Using BIS as a Controlled Variable During Anesthesia

Clara M. Ionescu*, *Student Member, IEEE*, Robin De Keyser, Bismark Claure Torrico, Tom De Smet, Michel MRF Struys, and Julio E. Normey-Rico

***Abstract*—This paper presents the application of predictive control to drug dosing during anesthesia in patients undergoing surgery. The performance of a generic predictive control strategy in drug dosing control, with a previously reported anesthesia-specific control algorithm, has been evaluated. The robustness properties of the predictive controller are evaluated with respect to inter- and intrapatient variability. A single-input (propofol) single-output (bispectral index, BIS) model of the patient has been assumed for prediction as well as for simulation. A set of 12 patient models were studied and interpatient variability and disturbances are used to assess robustness of the controller. Furthermore, the controller guarantees the stability in a desired range. The applicability of the predictive controller in a real-life environment via simulation studies has been assessed.**

***Index Terms*—Anesthesia, constraints, drug dosing control, model-based predictive control, nonlinear model, robustness.**

I. Introduction

DURING the last decade, the control technology has successfully influenced modern medicine through robotic surgery, electrophysiological system life support, and image-guided therapy and surgery [1]. Another area of medicine suited for applications of control is clinical pharmacology in general, and a particular case is the anesthesia and critical care unit medicine. Within this particular group of applications, monitoring and controlling the depth of anesthesia for patients during surgery offers interesting challenges to the control engineer [2].

This topic captured the attention of engineers and clinicians already decades ago [3], starting with expert systems that offer advice to the anesthesiologist upon optimal drug infusion rate during clinical trials [4]. It soon became clear that control of anesthesia poses a manifold of challenges, with multivariable characteristics [5], different dynamics depending on anesthetics substances [6], [7], and stability problems [8]. Further investigations proved propofol to be an anesthetic tackled well in control problems for hypnosis [9], [10], while recent studies showed that the control performance may also depend on the controlled variable [11], [12].

This paper presents a simulation study for the control of administration of propofol using the BIS as controlled variable. Propofol is an intravenous hypnotic providing a rapid onset time and relatively short duration of action, while the BIS (Aspect Medical Systems, Norwood, USA) is a commercially available measure of the effects of anesthetics and sedatives on the brain based on a bispectral analysis of the patient's EEG. It is important to realize that the BIS, like other measures such as midlatency auditory evoked potentials or entropy analysis of the EEG, is a surrogate measure for the depth of anesthesia as there is no direct measure available. Therefore, BIS will only be one of multiple indicators used by the anesthetist to safeguard the patient's wellbeing during an anesthetic procedure. In spite of these limitations, automated feedback control of propofol administration using the BIS as a controlled variable can serve as an automated pilot during long periods of surgery requiring a stable anesthetic, preserving the anesthetist's vigilance for critical events. The nonlinear response profile and inter- and intrapatient variation of the patient's hypnotic state to infusion of propofol should be handled by a robust controller. From a clinical point of view, an ideal controller would guide the induction of anesthesia in order to reach the target as fast as possible without initial overshoot. Afterwards, the controller would simply maintain the desired target as well as possible. Therefore, from control engineering viewpoint, model predictive control (MPC) plays a crucial role in solving such complex problems.

The original objective of the paper is threefold: 1) to compare the performance of a generic predictive control strategy, which is applied in drug dosing control, with a previously reported control algorithm specifically developed for anesthesia; 2) to evaluate via extensive simulation studies the robustness properties of the predictive controller with respect to inter- and intrapatient variability; and 3) to assess the applicability of the predictive anesthesia controller in a real-life clinical environment. In this contribution, the predictive control strategy extended prediction self-adaptive control (EPSAC) [13] is compared to a model adaptive controller for the control of depth of anesthesia. An overview of the models used for prediction and for control is

Manuscript received October 15, 2007; revised February 4, 2008. *Asterisk indicates corresponding author.*

*C. Ionescu is with the Department of Electrical Energy, Systems and Automation, Ghent University, B9000 Ghent, Belgium (e-mail: clara@autoctrl.UGent.be).

R. De Keyser is with the Department of Electrical Energy, Systems and Automation, Ghent University, B9000 Ghent, Belgium (e-mail: rdk@autoctrl.UGent.be).

B. Claure Torrico and J. E. Normey-Rico are with the Department of Automation and Systems, Federal University of Santa Catarina, Santa Catarina CEP 88040-970, Brazil (e-mail: bismark@das.ufsc.br; julio@das.ufsc.br).

T. De Smet is with DEMED Engineering, B-9140 Temse, Belgium (e-mail: tom.desmet@demed.be).

M. MRF Struys is with the Department of Anesthesia, University Medical Center Groningen, 9713 Groningen, The Netherlands and also with the Department of Anesthesiology, Ghent University, B9000 Ghent, Belgium (e-mail: michel.struys@ugent.be).

Color versions of one or more of the figures in this paper are available online at http://ieeexplore.ieee.org.

Digital Object Identifier 10.1109/TBME.2008.923142

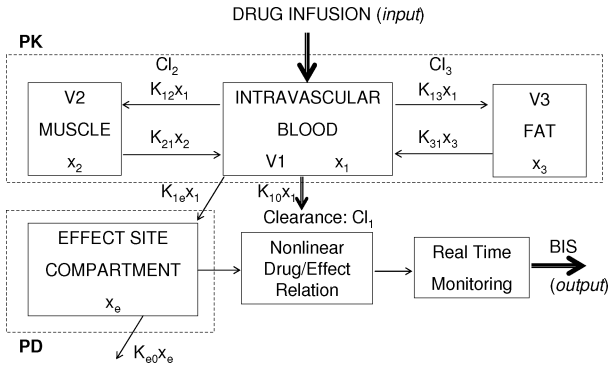

Fig. 1. Compartmental model of the patient, where PK denotes the pharmacokinetic model and PD denotes the pharmacodynamic model.

given in the next section. The EPSAC–MPC algorithm is described in Section III, and stability and robustness are analyzed in Section IV. The comparison between the model adaptive controller and another published controller was described earlier in the literature [14]. Closed-loop simulations for set point following and disturbance rejection are discussed in Section V. A conclusion section summarizes this comparison. A campaign of clinical trials has been approved in the meantime and scheduled for the coming year in the University Hospital Ghent, Belgium.

II. Realistic Patient Model

During anesthesia, when predictive control is intended for a precise administration of drugs, the model used in prediction becomes of vital importance. Such model must capture well enough the dynamics of the patient in response to the specific drug considered (in our case propofol). The relationship between drug infusion rate and the drug effect can be described with pharmacokinetic and pharmacodynamic models. Pharmacokinetic models describe the distribution of the drugs in the body and pharmacodynamic models describe the relationship between blood concentration of a drug and its clinical effect. Normally, these models can be identified for different kind of drugs by using a specific population of patients. For most anesthetic agents exist already several models [15]. When considering propofol as the manipulated drug, the pharmacokinetics can be described by a three-compartment model (see Fig. 1)

$$\begin{aligned}\dot{x}_1(t) &= -[k_{10}+k_{12}+k_{13}]x_1(t)+k_{21}x_2(t)\\ &\quad +k_{31}x_3(t)+u(t)\\ \dot{x}_2(t) &= k_{12}x_1(t)-k_{21}x_2(t)\\ \dot{x}_3(t) &= k_{13}x_1(t)-k_{31}x_3(t)\end{aligned} \tag{1}$$

where x_1 denotes the amount of drug in the central compartment (blood). The peripheral compartments two and three model the drug exchange of the blood with well and poorly perfused body tissues. The amount of drug in these compartments is denoted by x_2 and x_3, respectively. The constants k_{ji} for $j \neq i$ represent the drug amount transfer rate of drug from jth compartment to the ith compartment. The constant k_{10} is the rate of drug metabolism and $u(t)$ is the infusion rate of the anesthetic drug (propofol) into the central compartment (blood). From the drug amount in each compartment, the related concentrations are obtained by division with each compartment's volume. C_p is thus obtained by dividing x_1 with V_1 the central compartment's volume.

Multiple population models for propofol have been developed in the past. One popular model is the three-compartmental Schnider model for propofol [16], which calculates the constants using the following equations:

$$\begin{aligned}&V_1 = 4.27[l], \quad V_2 = 18.9-0.391(\text{age}-53)[l], \quad V_3 = 238[l]\\ &C_{l1} = 1.89+0.0456\,(\text{weight}-77)-0.0681(\text{lbm}-59)\\ &\qquad +0.0264(\text{height}-177)\\ &C_{l2} = 1.29-0.024\,(\text{age}-53), \quad C_{l3} = 0.836, \quad k_{10} = \frac{C_{l1}}{V_1}\\ &k_{12} = \frac{C_{l2}}{V_1}, \quad k_{13} = \frac{C_{l3}}{V_1}, \quad k_{21} = \frac{C_{l2}}{V_2}, \quad k_{31} = \frac{C_{l3}}{V_3}\end{aligned} \tag{2}$$

with lean body mass (lbm) MALE:

$$\text{lbm} = 1.1\,\text{weight} - 128\frac{\text{weight}^2}{\text{height}^2}.$$

Lbm FEMALE:

$$\text{lbm} = 1.07\,\text{weight} - 148\frac{\text{weight}^2}{\text{height}^2}.$$

As can be observed in (2), the values k_{10}, k_{12}, k_{13}, k_{21}, and k_{31} depend on the *mass* (in kilogram), *height* (in centimeter), *age* (in years), and *gender* of the patients. The other equation parameters and constants of (2) were identified for the propofol drug [24].

The pharmacodynamics are characterized by a first-order function related to the central compartment concentration C_p in blood

$$\dot{x}_e(t) = -k_{e_0}\,x_e(t)+k_{1_e}\,\dot{x}_1(t) \tag{3}$$

where k_{e0} and k_{1e} are constants and x_e is the amount of drug in the *effect compartment*. The effect compartment is defined as a negligibly small compartment connected to the central compartment. Assuming that the effect compartment is negligibly small, k_{1e} is an arbitrarily small fraction of k_{e0} [17]. Knowing k_{eo}, the apparent concentration in the effect compartment can be calculated since k_{eo} will precisely characterize the temporal effects of equilibration between the plasma concentration and the corresponding drug effect. Consequently, the equation is often used as

$$\dot{C}_e(t) = k_{e0}(C_p(t)-C_e(t)) \tag{4}$$

with C_e called the *effect-site compartment concentration*. For quantifying C_e during real-time monitoring, some commercial devices can be used. One of the devices used by clinicians to assess the depth of anesthesia is the BIS (Aspect Medical Systems, www.aspectms.com). The BIS monitor uses the EEG, closely related to the level of consciousness of the patient, to derive a monotonous measure of the depth of anesthesia ranging from 0 to 100 [1], [7]. The BIS can vary from 0 to 100. Zero means that the patient does not have cerebral activity (i.e., isoelectric EEG), and 100 denotes that the patient is fully awake AND conscious (e.g., for BIS $= 70$, the patient is conscious but sedated). When undergoing surgery, the desired BIS target is 50 and must remain

between 40 and 60, given that an adequate sedation is performed by the anesthesiologist. The BIS variable can be related to the drug effect concentration C_e by the empirical static but time-varying nonlinear relationship [1], called also the *Sigmoid* $E_{\max}$ *curve*

$$\mathrm{BIS}(t) = \left(\mathrm{E}_0 - \mathrm{E}_{\max}\frac{C_{\mathrm{e}}(t)^{\gamma}}{C_{\mathrm{e}}(t)^{\gamma} + \mathrm{C}_{50}^{\gamma}}\right) \tag{5}$$

where E_0 denotes the baseline (awake state—without drug) value, which, by convention, is typically assigned a value of 100, $E_{\max}$ denotes the maximum effect achieved by the drug infusion, C_{50} is the drug concentration at half maximal effect and represents the patient's sensitivity to the drug, and γ determines the steepness of the curve in (5). The effect site compartment that is connected to the central (C_p) compartment is given by

$$\dot{C}_e(t) = -0.456C_e(t) + 0.456C_p(t) \tag{6}$$

and the nominal patient model is completed.

III. EPSAC Approach to Model Predictive Control

Generally, an MPC algorithm consists of applying a control sequence that minimizes a multistage cost function of the form

$$J = \sum_{k=N_1}^{N_2}[y(t+k \mid t) - w(t+k)]^2 + \sum_{k=0}^{N_u-1}\lambda[\Delta u(t+k|t)]^2 \tag{7}$$

subject to

$$\begin{aligned} y_{\min} &\le y(t+k|t) \le y_{\max} && \forall k = 1,\ldots,N_2 \\ u_{\min} &\le u(t+k|t) \le u_{\max} && \forall k = 0,\ldots,N_u-1 \\ \Delta u_{\min} &\le \Delta u(t+k|t) \le \Delta u_{\max} && \forall k = 0,\ldots,N_u-1 \end{aligned} \tag{8}$$

where N_1 and N_2 are the minimum and maximum costing horizons, N_u is the control horizon, λ is the control weight, $w(t+k)$ is a future setpoint or reference sequence, $\Delta u(t)$ is the incremental control action, $\Delta = 1 - q^{-1}$, and $y(t+k \mid t)$ is the optimum k-step ahead prediction of the system output $y(t)$ on data up to time t.

A. Computing the Predictions

The process output can be represented as

$$y(t) = x(t) + n(t) \tag{9}$$

where $x(t)$ is the model output when is applied a control input $u(t)$ and $n(t)$ represents the effect of the disturbances and the modeling errors. The model output $x(t)$ is given by the generic dynamic system model

$$x(t) = f[x(t-1), x(t-2), \ldots, u(t-1), u(t-2), \ldots]. \tag{10}$$

Further on, the disturbance $n(t)$ can be modeled by

$$n(t) = \frac{C(q^{-1})}{D(q^{-1})}e(t) \tag{11}$$

where $e(t)$ is uncorrelated (white) noise with zero mean value, with $C(q^{-1})$ and $D(q^{-1})$ monic polynomials in the backward shift operator q^{-1} of form

$$\begin{aligned} C(q^{-1}) &= 1 + c_1q^{-1} + c_2q^{-2} + \cdots + c_{nc}q^{-nc} \\ D(q^{-1}) &= 1 + d_1q^{-1} + d_2q^{-2} + \cdots + d_{nd}q^{-nd}. \end{aligned}$$

The fundamental step in MPC methodology consists in predicting the process output at time instant t, indicated by $\{y(t+k|t), k = 1,\ldots,N_2\}$, over the prediction horizon N_2. Notice that since the definition of $y(t+k|t)$ implies that they are estimated (predicted) values, there is no need for explicit notation as $\hat{y}$. This observation applies also for the noise variable n and model output x. The prediction of the process output $y(t+k|t)$ is based on:

1) the measurements available at sampling time instant t

$$\{y(t), y(t-1), \ldots, u(t-1), u(t-2), \ldots\};$$

2) the future values of the input signal, calculated at time t

$$\{u(t|t), u(t+1|t), \ldots\}.$$

Using the generic process model (9), the predicted values of the output are

$$y(t+k|t) = x(t+k|t) + n(t+k|t). \tag{12}$$

In EPSAC [13], the prediction of $x(t+k|t)$ and $n(t+k|t)$ is done, respectively, by recursion of the process model (10) and by using filtering techniques on the noise model (11). In the case of linear models, the predictions can be done based on the diophantine equations [18].

B. Optimization Procedure

The optimization procedure is a crucial step in MPC algorithms. The numerical complexity depends on the characteristics of the models in terms of linearity, constraints, number of manipulated and controlled variables, etc. For linear models without constraints, there are some MPC techniques that solve the optimization procedure analytically [13], [19]. The solution can then be reduced to a linear controller of two degrees of freedom (DoFs) (see Fig. 3) [20], and it is important when analysis is performed. For nonlinear and linear models with constraints, it is not possible to find an analytical solution. However, there are several powerful optimization methods to solve the optimization problem using iterative procedures (Gauss–Newton method, the Levenberg–Marquardt method, or sequential quadratic programming) [21]. Either analytically, either by using iterative procedures, the optimal input sequence can be computed along the input horizon N_u. Nevertheless, due to the receding horizon strategy of MPC, only the optimal input $u(t)$ at the present moment is applied to the process, and, for the next sample period, the optimization problem is solved again.

From controller analysis standpoint, an analytical solution is important. For a special case $N_u = 1$, $N_1 = 1$, $N_2 = N$, and $\lambda = 0$, the optimal input is [13]

$$u(t) = (\mathbf{G}^T\mathbf{G})^{-1}\mathbf{G}^{\mathbf{T}}(\mathbf{w} - \mathbf{y_b}) = \mathbf{k}(\mathbf{w} - \mathbf{y_b}) \tag{13}$$

where $\mathbf{k}$ is a constant vector with dimension $1 \times N$, $\mathbf{w}$ is a vector that contains the future reference, $\mathbf{y_b} = [y_b(t+1|t), \ldots, y_b(t+$

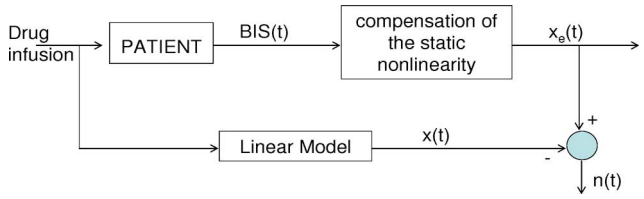

Fig. 2. Resulted linear patient model structure by compensating the static nonlinearity with a nominal BIS curve. See text for explanations.

$N|t)]^T$ (or base output) is a vector that contains the output prediction for an input $u(t+k|t)=0, \forall k=0,\ldots,N-1$. Based on diophantine equations, a matrix representation of $\mathbf{y_b}$ can be obtained

$$\mathbf{y_b} = \mathbf{F}\mathbf{y_p} + \mathbf{G_p}\mathbf{u_p}$$

$$\mathbf{F} = \begin{bmatrix} f_{1,1} & f_{1,2} & \cdots & f_{1,n_a+1} \\ f_{2,1} & f_{2,2} & \cdots & f_{2,n_a+1} \\ \vdots & \vdots & \ddots & \vdots \\ f_{N,1} & f_{N,2} & \cdots & f_{N,n_a+1} \end{bmatrix}, \quad \mathbf{y_p} = \begin{bmatrix} y(t) \\ y(t-1) \\ \vdots \\ y(t-n_a) \end{bmatrix}$$

$$\mathbf{G_p} = \begin{bmatrix} g'_{1,1} & g'_{1,2} & \cdots & g'_{1,n_b} \\ g'_{2,1} & g'_{2,2} & \cdots & g'_{2,n_b} \\ \vdots & \vdots & \ddots & \vdots \\ g'_{N,1} & g'_{N,2} & \cdots & g'_{N,n_b} \end{bmatrix}, \quad \mathbf{u_p} = \begin{bmatrix} u(t-1) \\ u(t-2) \\ \vdots \\ u(t-n_b) \end{bmatrix}.$$

The control input (13) becomes:

$$u(t) = \mathbf{kw} - \mathbf{kF}\mathbf{y_p} - \mathbf{kG_p}\mathbf{u_p} = k_w w(t) - (P_y(q^{-1})y(t) + P_u(q^{-1})u(t-1)) \quad (14)$$

where $k_w = \sum_{i=1}^{n_k} \mathbf{k}(i)$ and P_y, P_u are polynomials in the backward shift operator q^{-1}.

IV. Robustness and Stability Analysis

The nonlinearity introduced by the BIS variable is compensated by using the inverse of the referenced Sigmoid curve (5) and a linear model for the MPC controller is obtained (see Fig. 2).

In the prediction model, the controller uses the nominal Sigmoid curve, independent on the patients that are tested in simulation. This assumes that the controller is robust enough to compensate the interpatient variability. Notice that external disturbances such as surgical stimulation and blood loss are also present. Several approaches on stability and robustness analysis can be found in literature for MPC controllers. However, the analysis is not so trivial when constraints apply or nonlinear models are used.

In this application, the only constraints used are on the manipulated input (propofol infusion rate) as follows: minimum flow rate of zero and maximum flow rate of 3.3 mg/s. Hitherto, no output constraints were necessary, because for all simulated patients, the BIS values remain within acceptable limits agreed by anesthesiologists. The specific case with constraints on the input ($0 \le u \le sat$) is studied for the control horizon $N_u = 1$ and the prediction horizons N_1 and N_2 used as tuning parameters. Notice that for $N_u = 1$, the constrained MPC controller is equivalent to *clipping*, a case valid only for monovariable systems [13]. The term *clipping* assumes that the predictive controller does not take into account constraints, while computing the optimal input rate to the process, but only afterward, performing *hard limitations* if constraints are violated.

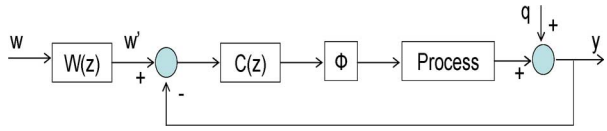

Fig. 3. Control scheme for two DoFs for the MPC strategy.

To study the stability and robustness, the block diagram of Fig. 3 is considered, since a linear MPC can be reduced in a 2-DoF controller for analysis purposes [20].

From (14), W and C can be computed to obtain the 2-DoF controller

$$W(z) = \frac{k_w}{P_y(z^{-1})}, \qquad C(z) = \frac{P_y(z^{-1})}{1 + z^{-1}P_u(z^{-1})}.$$

Additionally, there is a saturation nonlinearity at the input of the process ϕ (see Fig. 3). For stability analysis, the nonlinear element can be approximated by a *describing function*. It is valid for most of the processes with low-pass filter characteristics as is the case of the patient models. To obtain the *describing function*, first it is considered that the nonlinear element has the following input:

$$X\sin(\omega t)$$

since the output will be a nonlinear function, and it can be approximated by a Fourier series

$$Y_f(\omega t) = A_0 + \sum_{n=1}^{\infty}(A_n\cos(n\omega t) + B_n\sin(n\omega t)). \quad (15)$$

By definition, the *describing function* is given by

$$\phi = \frac{Y_1}{X}\angle\theta$$

where X is the amplitude of wave input, $Y_1 = \sqrt{A_1^2 + B_1^2}$, and $\theta = \tan^{-1}(A_1/B_1)$. For the case of saturation nonlinearity, the *describing function* is

$$\phi = \frac{2}{\pi}\left[\sin^{-1}\left(\frac{sat}{X}\right) + \frac{sat}{X}\sqrt{1 - \left(\frac{sat}{X}\right)^2}\right]$$

where $sat = 3.33$ is the amplitude of the saturation. From Fig. 3, the frequency closed-loop response is

$$\frac{y}{w'} = \frac{\phi L(j\omega)}{1 + \phi L(j\omega)}$$

where $L(j\omega) = P(j\omega)C(j\omega)$, P is the process or patient transfer function. The characteristic equation is $1 + \phi L(j\omega) = 0$ or $L(j\omega) = -1/\phi$.

Consider that L is *minimum phase* (as is the case for this drug dosing control application), according to the stability criteria, if

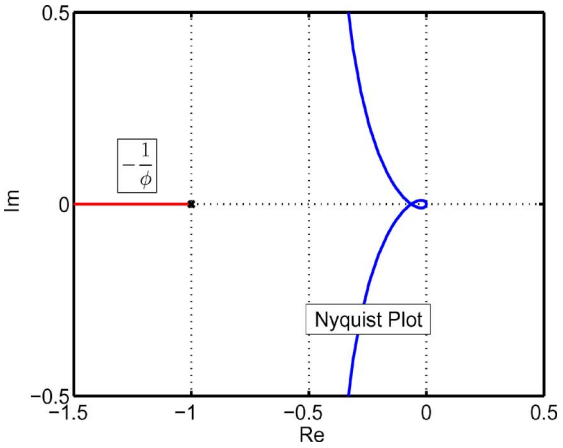

Fig. 4. Nyquist plot depicting the locus for $-1/\phi$ and the general patient model defined by $L(j\omega)$.

the locus of $L(j\omega)$ does not intersect the locus of $-1/\phi$, then the closed-loop system is stable. Otherwise, the system is unstable or presents a limit cycle.

Fig. 4 shows the locus of $-1/\phi$ for the case of saturation nonlinearity, it starts at -1 and goes to $-\infty$. There is a critical point at -1 that must be considered for stability analysis because if the locus of $L(j\omega)$ does not involve the critical point, then it will not intersect $-1/\phi$. Thus, the stability analysis is reduced to a linear analysis, and it means that if the closed-loop system without input saturation is stable, then it will remain stable under input saturation. Therefore, it is enough to consider the linear analysis tools for the stability and robustness.

The robustness analysis is performed considering that the modeling errors of the patient can be represented as unstructured uncertainties, that is, $P = P_n + \Delta P = P_n(1 + \delta P)$ with P_n the nominal patient. In order to maintain closed-loop stability under model uncertainties, the following relation must be satisfied [22]:

$$| \delta P(z) | < I_r(\omega) = \frac{| 1 + C(z)P_n(z) |}{| C(z)P_n(z) |} \tag{16}$$

for $\forall \omega \in (0, \pi/T_s)$, T_s is the sample time , $z = e^{j\omega}$, with $I_r(\omega)$ defined as the *robustness index* of the controller.

V. Results

In this section, the control performance is compared for the model-based adaptive controller versus the EPSAC–MPC controller. In addition, the robustness for the latter is observed.

A. Patients

The characteristics of these patients are given in Table I. The EPSAC controller design parameters are fixed for all patients and chosen as: $N_u = 1$, $N_1 = 1$, and $N_2 = 10$. Based on expertise, $N_u = 1$ is the most simple choice from practical engineering point of view, and it also gives satisfactory performance for stable processes. Moreover, our extensive simulation study indicated that the choices $N_u = 2$ and $N_u = 3$ did not result in improved performance. The value for N_1 is usually chosen

TABLE I
Characteristic Variables for Each of the 12 Patients Used in This Study. Patient Models Derived From Induction Data Only. Simulated Effect for Concentrations in Excess of 15 μg/ml will be Inaccurate, but Those Concentrations are not Attained During the Simulations

Patient	Age	Length	Weight	Gender	C_{50}	E_0	E_{max}	γ
1	40	163	54	F	6.33	98.80	94.10	2.24
2	36	163	50	F	6.76	98.60	86.00	4.29
3	28	164	52	F	8.44	91.20	80.70	4.1
4	50	163	83	F	6.44	95.90	102.00	2.18
5	28	164	60	M	4.93	94.70	85.30	2.46
6	43	163	59	F	12.10	90.20	147.00	2.42
7	37	187	75	M	8.02	92.00	104.00	2.10
8	38	174	80	F	6.56	95.50	76.40	4.12
9	41	170	70	F	6.15	89.20	63.80	6.89
10	37	167	58	F	13.70	83.10	151.00	1.65
11	42	179	78	M	4.82	91.80	77.90	1.85
12	34	172	58	F	4.95	96.20	90.80	1.84

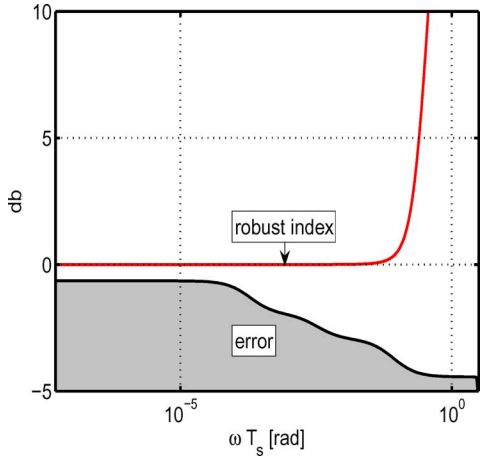

Fig. 5. Magnitude plot depicting robustness index for the gain of the nominal model and the error introduced by the interpatient variability.

equal to the dead-time index. In this simulation study, however, no dead time has been taken into account. Currently, in view of the planned clinical trials, the model and control strategy are extended to include significant dead time originating from the BIS measurement device. The value of N_2 is, as usual, chosen as a tuning parameter to tradeoff between fast response and robust stability.

The *nominal Sigmoid curve* parameters are chosen for the controller model: $C_{50} = 7.5$, $\gamma = 3$, $E_0 = 100$, $E_{\max} = 100$. The variability of the Sigmoid curve between the modeled patients and the prediction model in the controller can be seen as a variation on the gain. In the operating region (BIS:[40,60]), the gain varies from $1.6K$ to $0.5K$, where K is the gain of the model. For the set of patients considered in this investigation, Fig. 5 shows that $| \delta P(z) | < I_r(\omega)$, that is, the system is robustly stable.

Notice that in the EPSAC–MPC strategy presented in this paper, the changes in the Sigmoid curve during the surgery are not taken into account. In other words, a robust MPC controller is expected to tackle both inter- and intrapatient variability. Further

work will focus on an adaptive version of the controller, in order to take care of this variability in a more efficient way.

B. Model Adaptive Controller

In the next section, the EPSAC results will be compared to the results of a nonpredictive controller, which was specifically dedicated for automated anesthesia. The latter is a model adaptive controller, which uses a Bayesian method to tune a standard population curve to the responses for the specific patient. It has been described *in extenso* in [14], and, in the current paper, it will be further indicated by the acronym MAC.

Briefly, a medication delivery controller uses a patient response profile to determine a concentration of medication that will achieve the desired effect on the patient. The system estimates an individualized patient response profile using measured data points from induction phase (open-loop regimen), or it uses a population-based patient response profile. The patient-individualized relationship is applied during closed-loop control. A measure of the effect of the medication on the patient is continuously acquired by the system and stored. These data are used by the medication delivery controller in conjunction with past data to continuously recalculate the patient response profile. The reason for this adaptation is that the Sigmoid curve is changing not only from one patient to another, but it changes also during the surgery. The description of this controller does not make the scope of this paper, and therefore, the interested reader is referred to [14] for a comprehensive evaluation.

The MAC controller used in this comparison was tuned toward its use in an anesthesia environment, where fast response is preferred at the expense of acceptable undershoot values.

C. Closed-Loop Simulations

The evaluation of the control performance was described and applied previously [24], [23]. BIS was defined as the controlled variable, and the BIS target interval was set at [45,55]. This range is in accordance with the manufacturer's recommendations that the BIS has an accuracy of $+/-5$ BIS units. The results should be interpreted keeping in mind a standard BIS operating range for general anesthesia ranging 40–60. Sedation procedures would typically aim at a BIS target around 70, while a BIS level of 30 represents deep anesthesia. Obviously, it should be kept in mind that the BIS is a surrogate measurement for the hypnotic component of anesthesia, which will be observed by the anesthetist in combination with the patient's other vital signs. It should be noted as well that the amplitude of the BIS excursions is mainly determined by the stimulation profile used for challenging the controllers, applying sudden changes in BIS offset of up to 30 BIS units. As such, the absolute level of the BIS peaks is less relevant than the statistic evaluation of the resulting controller actions. The controller performance metrics are calculated on the measured values of the controlled variable (BIS) versus its target value and compared for MAC and MPC controllers. The performance of the controllers was evaluated during two periods: induction phase and maintenance phase. Hereby, induction is defined as the time between start of propofol administration until loss of consciousness, maintenance as the time between loss of consciousness and stop propofol infusion.

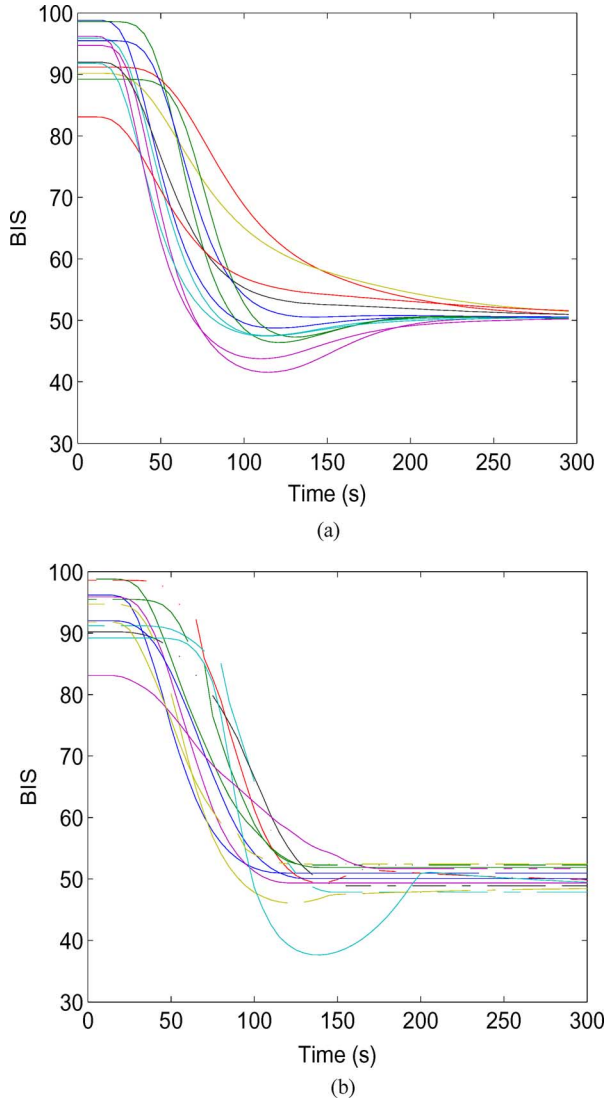

Fig. 6. Closed-loop response of the controlled variable (BIS) during anaesthesia induction phase with MPC and MAC strategies.

Fig. 6 shows the closed-loop simulations for the controlled output (BIS) for the MPC and MAC controllers in the first time interval, called the *induction* phase. In this phase, the BIS is brought to its reference value. The control performance over the family of patients is affected due to interpatient variability, when using a nominal model for prediction in the MPC strategy (ref. Section V-A). Notice that the MAC strategy includes an identification of the patient-specific parameters, and therefore, it takes into account the patient variability to obtain a better control performance. In the MPC strategy, this is not the case, the controller being designed based on a *nominal* patient model and robustness issues. Although the control strategies are significantly different, the average behavior of the controllers is similar. The difference best/worst in performance is better with the MAC controller, which is beneficial from an operation room management viewpoint. Notice, however, the intrinsic manner

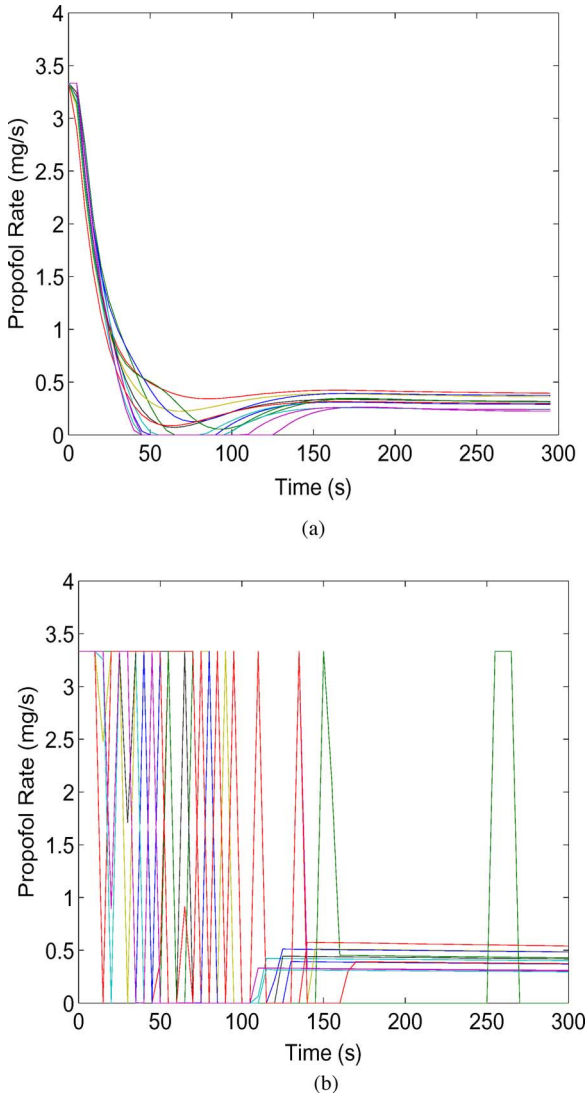

Fig. 7. Closed-loop response of the manipulated variable (propofol rate) during anaesthesia induction phase with MPC and MAC strategies.

in which the MPC tackles interpatient variability. Fig. 7 depicts the control effort corresponding to each strategy. From control engineer standpoint, the advantage of using MPC control is that a smooth convergence to the steady-state propofol rate is achieved. Although giving comparable performance, the MAC controller requires a more aggressive control signal, resulting in unusual peaks between clipping values.

The initial performance for BIS at induction was studied also statistically by using the following parameters (see Table II):

1) TT : observed time-to-target (in seconds) required for reaching first time the target interval of [55,45] BIS values;
2) $BIS\text{–}NADIR$: the lowest observed BIS value during induction phase;
3) ST : settling time on the reference BIS value, defined within $\pm$ 5 BIS (i.e., between 45 and 55 BIS) and stay within this BIS range; and
4) US : undershoot, defined as the BIS value that exceeds the limit of the defined BIS interval, namely, the 45 BIS value.

During the induction phase, the time-to-target for the EPSAC–MPC strategy has a rather high standard deviation value. The reason is that for patients p3 and p6, the controller brings asymptotically the BIS variable within the reference interval. The MAC controller brings the BIS variable to the reference BIS interval, but the price it pays for its speed is the aggressive control effort. The settling time ST for the EPSAC–MPC has also a high standard deviation value from its mean, due to the same asymptotical behavior. This result can be attributed to the fact that the EPSAC–MPC controller is a more *cautious* controller, making a tradeoff between small time-to-target, small undershoot and robustness against patient variability. The MAC controller overcomes this problem by making a patient-profile identification.

However, the control performance should be acceptable also during the surgery, as BIS is subject to disturbances. The evolution is depicted by Fig. 9 and Fig. 8 later.

In Fig. 8 and Fig. 9, the controlled and manipulated variable, respectively, are depicted for the MPC and MAC strategies. Both tests are subject to noise and disturbances, the latter being due to surgical intervention and blood loss. A statistical analysis was carried also in this case. First, the performance error was calculated according to the formula

$$\mathrm{PE} = \frac{\mathrm{BIS}_{\mathrm{measured}} - \mathrm{BIS}_{\mathrm{target}}}{\mathrm{BIS}_{\mathrm{target}}} \times 100. \tag{17}$$

Subsequently, median performance error (MDPE) representing the bias, median absolute performance error (MDAPE) representing inaccuracy, and wobble were calculated as described later. *MDPE* is a measure of bias and describes whether the measured values are systematically either above or below the target value. MDPE was calculated as

$$\mathrm{MDPE}_i = \mathrm{median} PE_{ij}, \qquad j-1,\ldots,N_i \tag{18}$$

where N_i is the number of values PE obtained for the ith subject. It should be noted that the MDPE indicates controller bias without revealing any information on dynamic or higher frequency behavior, nor on the amplitude of possible oscillations in control.

MDAPE reflects the inaccuracy of the control method in the ith subject

$$\mathrm{MDAPE}_i = \mathrm{median}|PE_{ij}|, \qquad j-1,\ldots,N_i \tag{19}$$

where N_i is the number of values $|PE|$ obtained for the ith subject.

Wobble is another index of the time-related changes in performance and measures the intrasubject variability in performance errors. In the ith subject, the percentage of wobble is calculated as follows:

$$\mathrm{Wobble}_i = \mathrm{median}|PE_{ij} - \mathrm{MDAPE}_i|, \qquad j-1,\ldots,N_i. \tag{20}$$

The overall control performance of MAC and EPSAC–MPC for BIS is shown in Table III. The performance error is similar in both the controllers. The MDAPE ($p = 0.2374$) and wobble ($p = 0.3567$) are equal in both the controllers. The MDPE is

TABLE II
CHARACTERISTIC INDEXES DURING INDUCTION-PHASE QUANTIFYING THE MAC AND EPSAC–MPC CONTROLLERS PERFORMANCE FOR EACH PATIENT, ALONG WITH THE MEAN VALUE (MEAN) AND STANDARD DEVIATION (STD). SEE TEXT FOR EXPLANATIONS

Index	Controller	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	Mean	STD
TT	MAC	90	120	120	125	95	90	130	105	115	100	145	100	111.25	17.33
	EPSAC	85	90	185	80	70	200	110	105	105	135	75	70	109.16	43.40
BIS-	MAC	50.96	51.87	49.04	47.86	49.35	46.1	48.87	50.06	52.27	37.63	51.70	52.42	49.01	4.06
NADIR	EPSAC	48.73	46.37	50.77	47.50	41.54	50.83	50.95	50.53	47.26	51.10	47.43	43.73	48.06	3.08
ST	MAC	90	120	120	125	95	90	130	105	115	190	145	100	118.75	28.13
	EPSAC	85	90	185	80	160	200	110	105	105	135	75	145	122.91	41.85
US	MAC	0	0	0	0	0	0	0	0	0	7	0	0	0.61	2.1
	EPSAC	0	0	0	0	3.45	0	0	0	0	0	0	1.26	0.39	1.01

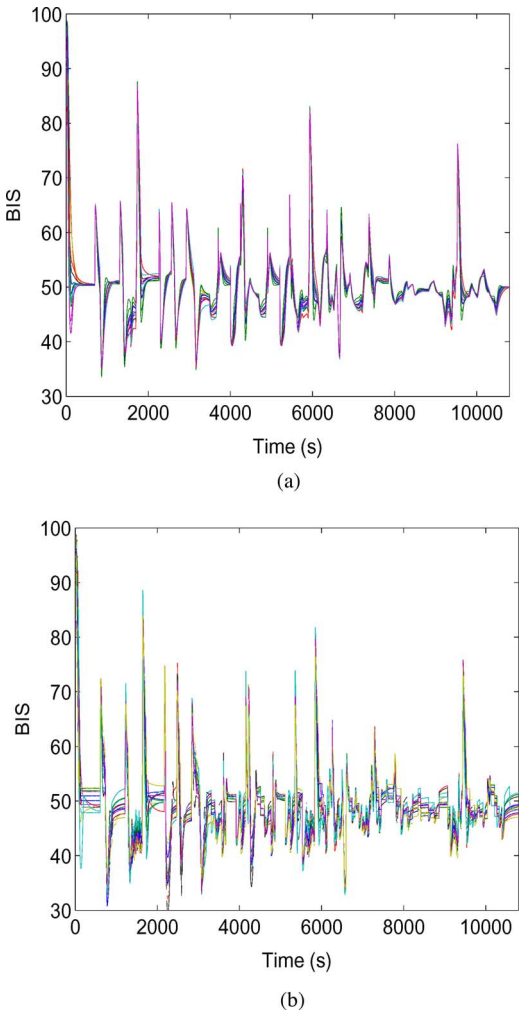

Fig. 8. Closed-loop response of the controlled variable (BIS) during entire surgery with MPC and MAC strategies.

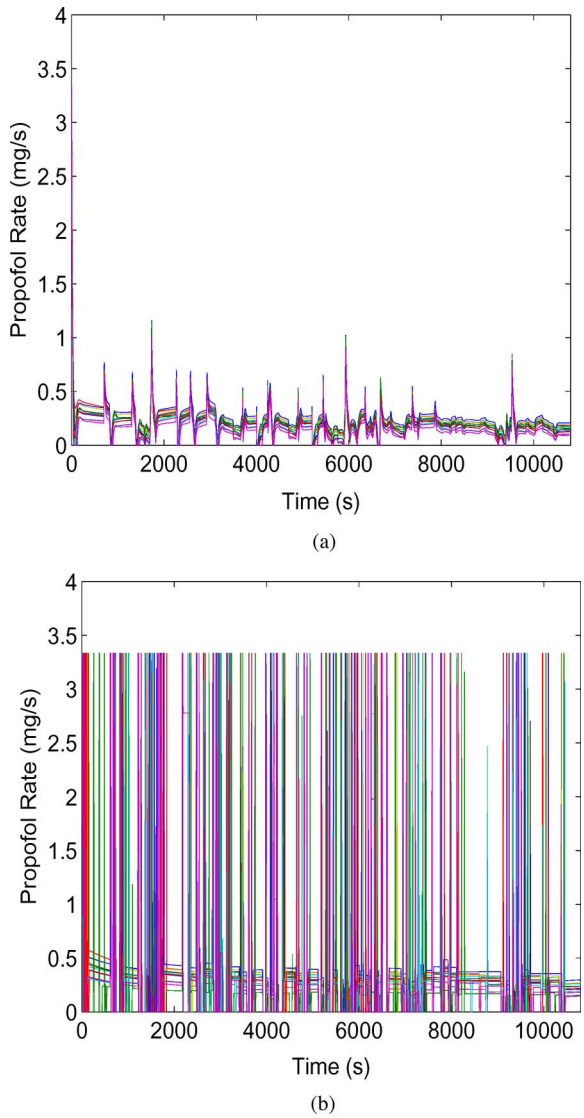

Fig. 9. Closed-loop response of the manipulated variable (propofol rate) during entire surgery with MPC and MAC strategies.

significantly different between both the controllers ($p < 0.0001$), with the MAC controller showing a more negative MDPE than the EPSAC controller. It should be noted that MDPE represents the direction (over- or undercontrol) of the performance errors rather than the size of the errors. A negative MDPE indicates that the controller tends to overdose, leading to BIS levels below target, whereas a positive MDPE might show the tendence of a too light anesthesia. The MDAPE is a necessary accompanying measure that does not indicate the sign of a possible bias, but describes both the amplitude of possible

TABLE III
OVERALL PERFORMANCE CHARACTERISTICS FOR THE MAC AND EPSAC–MPC CONTROLLERS

Index	Adaptive Bayesian	EPSAC
PE (%)	-1.76 ± 13.85	0.84 ± 13.03
MDPE (%)	-3.03 ± 0.82	-0.24 ± 0.14
MDAPE (%)	4.94 ± 0.75	4.62 ± 0.53
Wobble (%)	4.98 ± 1.08	4.65 ± 0.56

bias, as well as all other errors that prevent the controller from approaching the target. The MDAPE for both the controllers stays within 5%, which is acceptable from a clinical standpoint.

Furthermore, one should remember that closed-loop control for drug delivery is an essentially asymmetric control operation, since the controllers can only govern the infusion, not the elimination of drug from the body, which is a much slower process. Finally, it should be taken into account that the Bayesian MAC controller will ignore any BIS error less than ± 5, in accordance with the manufacturer's recommendations, whereas the EPSAC controller does take into account any BIS variation. Based on this knowledge, it can be interpreted that the two controllers show similar performance, each within its own control approach: the MAC controller will try to suppress any rise in BIS in a fast way, whereas the EPSAC controllers show a more gradual behavior. The expense for the MAC controller is that the BIS will drop below target, and, as the controller does not adjust the target once BIS is within ± 5, it has a negative offset for control.

A last observation is that the EPSAC–MPC controller is not tuned here for the disturbance rejection. The EPSAC disturbance filter (11), available for tuning specific disturbances, is not employed here to tackle the disturbances coming from surgery, or from modeling errors. It is left by default as a pure integrator, to ensure zero steady-state error results. Further research work is being scheduled in order to evaluate the benefits of such disturbance filter tuning.

VI. Conclusion

The contribution of this paper is threefold: 1) the performance comparison between a generic predictive control strategy and a previously reported control algorithm specifically developed for anesthesia; 2) the evaluation via extensive simulation studies the robustness properties of the predictive controller with respect to inter- and intrapatient variability; and 3) the assessment of the applicability of the predictive anesthesia controller in a real-life clinical environment. Specific for the EPSAC controller, due to the fact that the nonlinearity of the system consists of a static nonlinear gain, the closed-loop stability is guaranteed for the range where the gain varies due to interpatient variability. Both the controllers present a stable closed-loop behavior and titrated propofol administration accurately, resulting in BIS values in the reference interval. Also, they were able to induce the patients within clinical accepted time limits and with significant low undershoot. From clinical standpoint, both controllers perform well. The MAC controller shows a faster onset of response to rising BIS values, at the expense of more frequent peaks in the manipulated propofol rate than the EPSAC–MPC controller. If the offset filter in the MAC controller would be removed, the performance might result in a tighter control. However, in this comparative study, the MAC controller was used exactly as published previously [23], where it was compared to a classical PID controller, resulting in a gradual overview.

As a general remark, the tuning rules of the EPSAC–MPC controller are intuitive to attain some performance specifications. The EPSAC–MPC algorithm has been previously used in several real-life applications, making it suitable for use in clinical trials. The EPSAC–MPC performance can be improved by adding an adaptive gain scheduling in the first 200 s of the anesthesia, by varying the Sigmoid curve based on the real feedback data (BIS monitor). Also, the disturbance filter can be suitably tuned to reject specific disturbances and a recursive parameter estimation algorithm adapting to the specific characteristics of the patient is currently under research. A campaign of clinical trials has been approved in the meantime and scheduled for the coming year in the University Hospital Ghent, Belgium. Its results will provide the material for a consecutive paper.

References

[1] J. M. Bailey and W. M. Haddad, "Drug dosing control in clinical pharmacology," *IEEE Control Syst. Mag.*, vol. 25, no. 2, pp. 35–51, Apr. 2005.

[2] W. M. Haddad, T. Hayakawa, and J. M. Bailey, "Nonlinear adaptive control for intensive care unit sedation and operating room hypnosis," in *Proc. Am. Control Conf.*, vol. 2, 2003, pp. 1808–1813.

[3] D. O'Hara, D. Bogen, and A. Noordergraaf, "The use of computers for controlling the delivery of anesthesia," *Anesthesiology*, vol. 77, pp. 563–581, 1992.

[4] S. G. Greenhow, D. A. Linkens, and A. J. Asbury, "Pilot study of an expert system adviser for controlling general anesthesia," *Brit. J. Anesthesia*, vol. 71, pp. 359–365, 1993.

[5] S. Petersen-Felix, S. Hacisalihzade, A. M. Zbinden, and P. Feigenwinter, "Arterial pressure control with isoflurane using fuzzy logic," *Brit. J. Anesthesia*, vol. 74, pp. 66–72, 1995.

[6] M. Curatolo, M. Derighetti, S. Petersen-Felix, P Feigenwinter, M. Fisher, and A. M. Zbinden, "Fuzzy logic control of inspired isoflurane and oxygen concentrations using minimal flow anesthesia," *Brit. J. Anesthesia*, vol. 76, pp. 245–250, 1996.

[7] M. Struys, H. Vereecke, A. Moerman, E. W. Jensen, D. Verhaeghen, N. De Neve, F. Dumortier, and E. Mortier, "Ability of the bispectral index, autoregressive modelling with exogenous input-derived auditory evoked potentials, and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil," *Anesthesiology*, vol. 99, pp. 802–814, 2003.

[8] A. J. Asbury, "Feedback control in anesthesia," *Int. J. Clin. Monitoring Comput.*, vol. 14, pp. 1–10, 1997.

[9] J. W. Huang, Y. Y. Lu, A. Nayak, and R. Roy, "Depth of anesthesia estimation and control," *IEEE Trans. Biomed. Eng.*, vol. 46, no. 1, pp. 71–81, Jan. 1999.

[10] G. N. Kenny and H. Mantzaridis, "Closed-loop control of propofol anesthesia," *Brit. J. Anesthesia*, vol. 83, pp. 223–230, 1999.

[11] P. Mainland, B. Lee, T. G. Short, A. Morley, and J. Derrick, "Closed loop control of anesthesia: An assessment of the bispectral index as the target of control," *Anesthesia*, vol. 55, pp. 953–959, 2000.

[12] C. H. Ting, R. H. Arnott, D. A. Linkens, and A. Angel, "Migrating from target-controlled infusion to closed-loop control in general anesthesia," *Comput. Methods Programs Biomed.*, vol. 75, pp. 127–139, 2004.

[13] R. M. C. De, "Keyser Model Based Predictive Control," in *Invited Chapter in UNESCO Encyclopedia of Life Support Systems (EoLSS),* vol. 83. Oxford: Eolss Publishers, 2003, ISBN 0 9542 989 18-26-34, article 6.43.16.1.

[14] T. De Smet, M. M. R. F. Struys, S. Greenwald, E. P. Mortier, and S. L. Shafer, "Estimation of optimal modeling weights for a Bayesian-based closed loop system for propofol administration using the bispectral index as a controlled variable: A simulation study," *Anesth. Analg.*, vol. 105, pp. 1629–1638, 2007.

[15] A. Absalom and M. MRF Struys, *An Overview of TCI & TIVA*. New York: Academia, 2005.

[16] T. W. Schnider, C. F. Minto, P. L. Gambus, C. Andresen, D. B. Goodale, and E. J. Youngs, "The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers," *Anesthesiology*, vol. 88, pp. 1170–1182, 1998.

[17] S. L. Shafer, D. E. Longnecker, J. H. Tinker, and G. E. Morgan, "Principles of pharmacokinetics and pharmacodynamics," in *Principles and Practice of Anesthesiology*, 2nd ed. New York: McGraw-Hill, 1998.

[18] E. F. Camacho and C. Bordons, *Model Predictive Control*. New York: Springer-Verlag, 2003.

[19] D. W. Clarke, C. Mothadi, and P. S. Tuffs, "Generalized predictive control. Part I the basic algorithm and Part II extensions and interpretations," *Automatica*, vol. 23, pp. 137–160, 1987.
[20] J. E. Normey-Rico and E. F. Camacho, "Robustness effects of a prefilter in Smith predictor based generalised predictive controller," *IEE Proc., Control Theory Appl.* 1999, vol. 146, pp. 179–185.
[21] L. T. Biegler, "Advances in nonlinear programming concepts for process control," *J. Process. Control*, vol. 8, pp. 301–311, 1998.
[22] S. Skogestad and I. Postlethwaite, *Multivariable Feedback Control. Analysis and Design*. New York: Wiley, 1996.
[23] M. Struys, T. De Smet, S. Greenwald, A. Absalom, S. Bing, and E. Mortier, "Performance evaluation of two published closed-loop control systems using bispectral index monitoring," *Anesthesiology*, vol. 100, pp. 640–647, 2004.
[24] M. Struys, T. De Smet, L. Versichelen, S. Van de Velde, R. Van den Broecke, and E. Mortier, "Comparison of closed loop controlled administration of propofol using bispectral index as the controlled variable versus standard practice controlled administration," *Anesthesiology*, vol. 95, pp. 6–17, 2001.

Clara M. Ionescu (S'06) received the M.Sc. degree in industrial informatics and automation from "Dunarea de Jos" University, Galati, Romania, in 2003. She is currently working toward the Ph.D. degree at Ghent University, Ghent, Belgium, in the human respiratory system with noninteger order models.

She is involved in several international projects, with both industrial and biomedical applications, for identification and control. Her current research interests include biomedical applications, with identification and advanced control objectives.

Robin De Keyser received the M.Sc. degree (great distinction + Boulvin-Prize) in electromechanical engineering and the Ph.D. degree (the greatest distinction) with a thesis on "design and application of self-tuning controllers" in control engineering from the Ghent University, Ghent, Belgium, in 1974 and 1980, respectively.

He is currently a Full Professor of Control Engineering at the Faculty of Engineering, Ghent University, Ghent, Belgium. He was an external Review Expert in several European Commission research programmes and is one of the pioneers who produced the original concepts of "predictive control" during the 1980s. He is the author or coauthor of about 250 papers published in journals, books, and conference proceedings. His current research interests include model predictive control, autotuning and adaptive control, modeling and simulation, system identification, and pilot implementations in technical and nontechnical systems, such as chemical, steel, marine, mechatronic, semiconductor, power electronics, and biomedical.

Bismark Claure Torrico was born in Cochabamba, Bolivia, in 1977. He received the Ph.D. degree in electrical engineering from the Federal University of Santa Catarina (UFSC), Santa Catarina, Brazil, in 2007.

He is currently a Postdoctoral Researcher at the UFSC. His current research interests include robust model predictive controllers, dead time compensators, and time delay systems.

Tom De Smet received the M.Sc. degree in electronics from Ghent University, Ghent, Belgium, in 1995.

He is currently the Chief Executive Officer (CEO) of DEMED Engineering, Temse, Belgium, and a Consultant to the Department of Anesthesia, Ghent University. He is also the driving force behind Rugloop, a software package facilitating synchronous data capture for research. He current research interests include pharmacokinetic and dynamic modelling, drug administration technology, and automation in drug administration.

Michel MRF Struys received the M.D. degree in 1992 and the Ph.D. degree (the greatest distinction) with a thesis on "A study on: optimal dosing of anesthetics-hypnotics during anesthesia and sedation" for Doctor in Medical Sciences from Ghent University, Ghent, Belgium, in 1998.

He is currently Professor and Chair at the Department of Anesthesiology, University Medical Center Groningen (UMCG), Groningen, The Netherlands and a Professor of Anesthesiology, Department of Anesthesiology, Ghent University, Ghent, Belgium. He is also a Certified Clinical Pharmacologist. His current research interest includes clinical pharmacology in anaesthesia, pharmacometrics, drug administration techniques, and equipment and neuro-monitoring.

Julio E. Normey-Rico was born in Montevideo, Uruguay, in 1962. He received the Ph.D. degree from the Department of System Engineering and Automatic Control, University of Seville, Seville, Spain, in 1999.

He is currently an Associated Professor at the Department of Automation and Systems Engineering, Federal University of Santa Catarina (UFSC), Santa Catarina, Brazil. His current research interests include robust model predictive controllers, dead time compensators, and time delay systems. He is the author or coauthor of about 100 conference and journal papers, the book *Control of Dead-Time Processes* (Springer, 2007), and supervised 20 Ph.D./M.Sc. graduates.