Robustness Tests of a Model Based Predictive Control Strategy for Depth of Anesthesia Regulation in a Propofol to Bispectral Index Framework

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Abstract— **This paper verifies the robustness of a model based predictive control scheme for depth of anesthesia (DOA) regulation. The manipulated variable is Propofol, which is used in a Model based Predictive Control (MPC) algorithm for automatic induction and control of DOA. In turn, DOA is evaluated by means of the Bispectral index (BIS). The simulation tests are performed on a set of 17 virtually generated realistic patients with significantly varying sensitivity to Propofol infusion. The results show a high-efficiency, optimal dosage and robustness of the MPC algorithm to induce and maintain the desired BIS reference while rejecting typical disturbances from surgery.**

Keywords— **Depth of anesthesia (DOA), predictive control, propofol, bispectral index, robustness.**

I. Introduction

General anesthesia plays an important role in surgery and intensive care unit and requires critical assessment of induced quantities of drugs into the patient. There are three major interactive parts in anesthesia: sedation, analgesia and neuromuscular blockade.

Usually, anesthesiologists control the drug dosing during anesthesia by monitoring hemodynamic signals. This open-loop technique reaches the target level of sedation fast, but it may result in minimal values (undershoot) which are not safe for the patient. On the other hand, if the drug delivery regulation is done automatically, anesthesiologists will have more time to concentrate on critical issues that may threaten the safety of the patient. Control of anesthesia poses a manifold of challenges: multivariable characteristics, variable time delays, inter- and intra-patient variability, dynamics dependent on anesthetic substances and stability issues [1], [2]. Numerous PID controllers have been designed during decades, but since these controllers cannot anticipate the response of the patient and do not have any prior knowledge of the drug metabolism, the performances were sub-optimal. Therefore, model based strategies using fuzzy [3], adaptive [1] and predictive [4] control algorithms have been developed and applied in clinical trials.

In this paper, we present a single input (Propofol) – single output (bispectral index) model based predictive control (MPC) algorithm for controlling the depth of anesthesia. The patient models for prediction and for simulation purposes are given in the second section, followed by the description of the control algorithm. The closed loop results are given in the fourth section for induction of anesthesia and for maintenance within clinically acceptable values while rejecting typical surgery disturbances.

II. Patient model

A. The Pharmacokinetic-Pharmacodynamic Model

Propofol is a hypnotic agent, for which the pharmacologic properties have been well described and studied in different kind of patients. Given its beneficial pharmacological profile, Propofol is used as one of the drugs of choice for both induction and maintenance of the hypnotic component of anesthesia and intensive care sedation . This drug is the input of the patient model and the output is the Bispectral Index (BIS), a signal derived from the electroencephalogram (EEG). Using EEG, several derived, computerized parameters like the BIS have been tested and validated as a promising measure of the hypnotic component of anesthesia [5]. BIS values lie in the range of 0-100; whereas 90-100 range represents fully awake patients; 60-70 range and 40-60 range indicate light and moderate hypnotic state, respectively. For the induction phase of DOA, a BIS value of 50 is considered suitable.

In figure 1 the pharmacokinetic (PK) – pharmacodynamic (PD) blocks denote the 4th order compartmental model for Propofol [6], [7]. Compartmental models are used to represent the distribution of drugs in the body, i.e. mass balance. In each compartment the drug concentration is assumed to be uniform, as in a perfect and instantaneous mixing:

$$\begin{aligned}
&\dot{x}_1(t) = -\left[k_{10} + k_{12} + k_{13}\right] \cdot x_1(t) + k_{21} \cdot x_2(t) \\
&+ k_{31} \cdot x_3(t) + u(t) \\
&\dot{x}_2(t) = k_{12} \cdot x_1(t) - k_{21} \cdot x_2(t) \\
&\dot{x}_3(t) = k_{13} \cdot x_1(t) - k_{31} \cdot x_3(t) \\
&\dot{x}_e(t) = -k_{e0} \cdot x_e(t) - k_{1e} \cdot x_1(t)
\end{aligned} \tag{1}$$

S. Vlad and R.V. Ciupa (Eds.): MEDITECH 2011, IFMBE Proceedings 36, pp. 234–239, 2011.
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where x_1 [mg] denotes the amount of drug in the central compartment. The blood concentration is expressed by x_1/V_1. The peripheral compartments 2 and 3 model the drug exchange of the blood with well and poorly diffused body tissues. The masses of drug in fast and slow equilibrating peripheral compartments are denoted by x_2 and x_3 respectively. The parameters k_{ij} for $i \neq j$, denote the drug transfer frequency from the i^{th} to the j^{th} compartment and $u(t)$ [mg/s] is the infusion rate of the anesthetic drug into the central compartment. The parameters k_{ij} of the PK models depend on age, weight, height and gender and can be calculated for propofol:

$$V_1 = 4.27 \ [l], V_2 = 18.9 - 0.391 \cdot (age - 53) \ [l], V_3 = 2.38 \ [l]$$

$$C_{l1} = 1.89 + 0.0456(weight - 77) - 0.0681(lbm - 59) + \\ + 0.0264(height - 177) \ [l/\min]$$

$$C_{l2} = 1.29 - 0.024(age - 53) \ [l/\min], C_{l3} = 0.836 \ [l/\min]$$

$$k_{10} = \frac{C_{l1}}{V_1} \left[\min^{-1}\right], k_{12} = \frac{C_{l2}}{V_1} \left[\min^{-1}\right], k_{13} = \frac{C_{l3}}{V_1} \left[\min^{-1}\right],$$

$$k_{21} = \frac{C_{l2}}{V_2} \left[\min^{-1}\right], k_{31} = \frac{C_{l3}}{V_3} \left[\min^{-1}\right]$$

where C_{l1} is the rate at which the drug is cleared from the body, and C_{l2} and C_{l3} are the rates at which the drug is removed from the central compartment to the other two compartments by distribution. The lean body mass (lbm) for men and women have the following expressions:

$$1.1 \cdot weight - 128 \cdot \frac{weight^2}{height^2}$$

and

$$1.07 \cdot weight - 148 \cdot \frac{weight^2}{height^2},$$

respectively.

An additional hypothetical effect compartment was proposed to represent the lag between drug plasma concentration and drug response. The concentration of drug in this compartment is represented by x_e. The effect compartment receives drug from the central compartment by a first-order process and it is regarded as a virtual additional compartment. Therefore, the drug transfer frequency from the central compartment to the effect site-compartment is equal to the frequency of drug removal from the effect-site compartment: $k_{e0}=k_{1e}=0.456$ [min^{-1}]. Knowing k_{e0}, the apparent concentration in the effect compartment can be calculated since k_{e0} will precisely characterize the temporal effects of equilibration between the plasma concentration and the corresponding drug effect. Consequently, the equation is often used as:

$$\dot{C}_e(t) = k_{e0} \cdot (C_e(t) - C_p(t)) \qquad (2)$$

with C_e called the *effect-site compartment concentration*,. The BIS variable can be related to the drug effect concentration C_e by the empirical static but time varying nonlinear relationship [4], called also the *Hill curve:*

$$BIS(t) = E_0 - E_{\max} \cdot \frac{C_e(t)^{\gamma}}{C_e(t)^{\gamma} + EC_{50}^{\gamma}} \qquad (3)$$

where E_0 denotes the baseline value (awake state - without drug), which by convention is typically assigned a value of 100, E_{max} denotes the maximum effect achieved by the drug infusion, EC_{50} is the drug concentration at half maximal effect and represents the patient sensitivity to the drug, and γ determines the steepness of the curve. The constant k_{10}

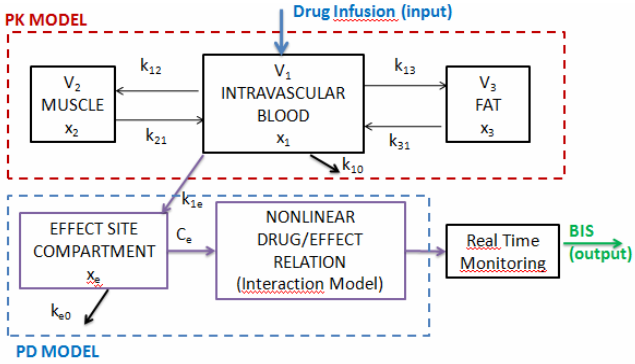

Fig. 1 Compartmental model of the patient, where PK denotes the pharmacokinetic model and PD denotes the pharmacodynamic model.

B. *Nominal Patient Model Parameters*

A set of model parameter values for the nominal patient are necessary in order to be used for prediction purposes. For comparison purposes, the same nominal patient as that given in [8] will be used in this study. The corresponding model parameters are given in Table 1.

Table 1 Values of the parameters for the nominal patient used for prediction of BIS values based on known Propofol infusion rates.

parameter	value
k_{10} (min^{-1})	0.119
k_{12} (min^{-1})	0.112
k_{21} (min^{-1})	0.055
k_{13} (min^{-1})	0.0410
k_{31} (min^{-1})	0.0033
V_1 (l)	5.05
V_2 (l)	30.6
V_3 (l)	191.1

Table 2 Values of the parameters for the 17 patient set arranged in decreasing order of the BIS sensitivity to Propofol infusion [8].

Patient no.	Parameter							
	k_{10}	k_{12}	k_{21}	k_{13}	k_{31}	k_{e0}	EC_{50}	γ
1 (sensitive)	0.08925	0.084	0.06875	0.031425	0.004125	0.459	1.6	2
2	0.14875	0.14	0.04125	0.052375	0.004125	0.239	1.6	2
3	0.14875	0.112	0.04125	0.0419	0.004125	0.239	1.6	3.122
4	0.14875	0.14	0.04125	0.052375	0.004125	0.239	1.6	3.122
5	0.08925	0.084	0.04125	0.052375	0.002475	0.459	2.65	2.561
6	0.08925	0.084	0.06875	0.031425	0.002475	0.349	2.65	2.561
7	0.14875	0.112	0.06875	0.031425	0.002475	0.459	2.65	2.561
8 (nominal)	0.119	0.112	0.055	0.0419	0.0033	0.349	2.65	2.561
9	0.119	0.112	0.055	0.0419	0.0033	0.239	2.65	2
10	0.119	0.112	0.055	0.0419	0.0033	0.239	2.65	2.561
11	0.08925	0.084	0.06875	0.031425	0.002475	0.459	3.7	2
12	0.14875	0.112	0.06875	0.031425	0.002475	0.349	3.7	2.561
13	0.08925	0.084	0.06875	0.031425	0.002475	0.239	3.7	2.561
14	0.08925	0.084	0.06875	0.031425	0.002475	0.239	3.7	3.122
15	0.08925	0.084	0.04125	0.052375	0.002475	0.239	3.7	3.122
16	0.14875	0.14	0.04125	0.052375	0.004125	0.349	3.7	2.561
17 (insensitive)	0.14875	0.14	0.04125	0.052375	0.002475	0.239	3.7	3.122

C. *Population Database*

The population database consisted of 17 virtually generated realistic patients, whose model parameter values are given in Table 2. These values are taken from [8] and based on a statistical analysis on inter-patient variability. These 17 patient relevant sets are arranged in the decreasing order of their BIS sensitivity to the amount of propofol infusion. For the **insensitive patient**, the rates in the central compartment k_{10}, k_{12} and k_{13} are high (0.149, 0.14 and 0.052, respectively) and the k_{21} and k_{31} rate constants are low (0.041 and 0.002, respectively). In the PD parameters, higher EC_{50} (3.7) indicates the need for more drug to get to the same hypnosis level, higher γ (3.12) indicates higher nonlinearity (slope in the Sigmoid Hill curve) and lower k_{e0} (0.239) indicates sluggishness in response. For the **sensitive patient** k_{10}, k_{12} and k_{13} are low (0.089,0.084 and 0.031, respectively) and the k_{21} and k_{31} rate constants are high (0.069 and 0.004, respectively). In the PD parameters, lower EC_{50} (1.6) indicates the need for less drug to get to the same hypnosis level, lower γ (2) indicates lower nonlinearity (slope in the Sigmoid Hill curve) and higher k_{e0} (0.459) indicates faster response. With these patients at hand, robustness of the control algorithm can be tested.

III. The EPSAC-MPC Approach

A. *Controller Design*

In the general MPC scheme represented in figure 2, the patient model is used to predict the current value of the output variable (BIS). The difference between the measured BIS from the patient and the model output (residual), serves as feedback signal in the prediction block. With this residual and the input u, the prediction block predicts the future values of the output BIS. On the basis of these predicted BIS values, the controller calculates the future optimal infusion rates over a number of samples in the future, called the prediction horizon. However, only the first calculated sample is applied to the process (i.e. principle of receding horizon).

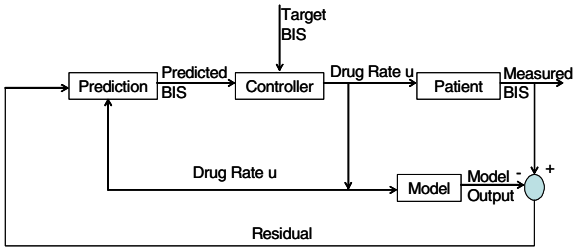

Fig. 2 MPC scheme for closed loop BIS regulation

In this paper, we apply the EPSAC (Extended Prediction Self-Adaptive Control) strategy described in detail in [9]. The EPSAC-MPC is based on a generic process model:

$$y(t) = x(t) + n(t) \tag{4}$$

The disturbance $n(t)$ includes the effects in the measured output $y(t)$ which do not come from the model input $u(t)$ via the available model. These non-measurable disturbances have a stochastic character with non-zero average value, which can be modeled by a colored noise process:

$$n(t) = \left[C(q^{-1}) / D(q^{-1}) \right] \cdot e(t) \tag{5}$$

with: $e(t)$ - uncorrelated (white) noise with zero mean value; $C(q^{-1})$ and $D(q^{-1})$ - monic polynomials in the backward shift operator q^{-1} of orders n_c and n_d. In this application, the disturbance filter $C(q^{-1}) / D(q^{-1})$ is defined as a pure integrator. The relationship between $u(t)$ and $x(t)$ is given by the generic dynamic system model:

$$x(t) = f\left[x(t-1), x(t-2), \cdots, u(t-1), u(t-2), \cdots \right] \tag{6}$$

In our case the input applied to the patient, $u(t)$, represents the Propofol delivery rate. The model output is then represented by:

$$x(t) = m_1 \cdot C_{e\Pr op}(t - T_d) + m_2 \cdot C_{e\mathrm{Re}m}(t - T_d) \tag{7}$$

The process output is predicted at time instant t over the prediction horizon N_2, based on the measurements available at that moment and the future outputs of the control signal. The predicted values of the output are:

$$y(t+k/t) = x(t+k/t) + n(t+k/t) \tag{8}$$

Prediction of $x(t+k|t)$ and of $n(t+k|t)$ can be done respectively by recursion of the process model and by using filtering techniques on the noise model (5) [9]. In EPSAC for linear models, the future response is considered as being the cumulative result of two effects:

$$y(t+k/t) = y_{base}(t+k/t) + y_{opt}(t+k/t) \tag{9}$$

where $y_{base}(t+k/t)$ represents:

- effect of past control $\{u(t\text{-}1),\ u(t\text{-}2),\ \ldots\}$ (initial conditions at time t);
- effect of a *base* future control scenario, called $u_{\mathrm{base}}(t+k|t),\ \ k \geq 0$, which is defined *a priori*; for linear systems the choice is irrelevant, a simple choice being $\left\{ u_{\mathrm{base}}(t+k|t) \equiv 0,\ \ k \geq 0 \right\}$;
- effect of future (predicted) disturbances $n(t+k|t)$.

while, $y_{opt}(t+k/t)$ represents:

- effect of the *optimizing* future control actions $\left\{ \delta u(t|t),\ \ \delta u(t+1|t),\ \ \ldots\ \ \delta u(t+N_u-1|t) \right\}$ with $\delta u(t+k|t) = u(t+k|t) - u_{\mathrm{base}}(t+k|t)$. The *design* parameter N_u, called the *control horizon* (a well-known concept in MPC-literature), is considered in this paper equal to 1.

The controller output is obtained by minimizing a cost function. The basic cost function is:

$$J(\mathbf{U}) = \sum_{k=N_1}^{N_2} \left[r(t+k/t) - y(t+k/t) \right]^2 \tag{10}$$

where $r(t+k/t)$ is the desired *reference trajectory*. The cost function (10) is a quadratic form in **U,** which leads after minimization w.r.t. **U** to the optimal solution:

$$\mathbf{U}^* = \left[\mathbf{G}^T \cdot \mathbf{G} \right]^{-1} \mathbf{G}^T \cdot (\mathbf{R} - \bar{\mathbf{Y}}) \tag{11}$$

with **R** the reference trajectory,

$$\overline{\mathbf{Y}} = \left[Y_{base}(t+N_1/t) \ldots\ldots Y_{base}(t+N_2/t) \right]^T$$

$$\mathbf{U} = \left[\delta u(t/t) \ldots\ldots \delta u(t+N_u-1/t) \right]^T \text{ and}$$

$$\mathbf{G} = \begin{bmatrix} g\mathrm{Prop}_{N_1} \\ \ldots \\ g\mathrm{Prop}_{N_2} \end{bmatrix}$$

where $g\mathrm{Prop}_{N_1}$ …. $g\mathrm{Prop}_{N_2}$ are the coefficients of the unit step response of the PK-PD propofol model. The EPSAC strategy was implemented to control the value of BIS, using the PK-PD model presented from (1), (2) and (3). The prediction model was used with the nominal values from table 1, while each patient was simulated with the values from table 2. In this way, significant modeling errors are introduced in the control scheme, accounting for inter-patient variability. In this study, the MPC control parameters are set to: N_1=1, N_u=1 and a sampling time for control action every 5 seconds.

B. Performance Evaluation

In order to evaluate the performance in the closed loop, we introduce the index defined by

$$IAE = \int_0^{\tau} \left| R(\tau) - BIS(\tau) \right| d\tau \tag{12}$$

with $R(\tau)$ the desired reference BIS value, in this case set to BIS=50, BIS(τ) the real output of the patient and τ the time instant. Notice that the index defined in (12) is known as the integral absolute error (IAE).

Next, it is important to introduce realistic disturbances, in this case typical surgery stimuli. A standard stimulus profile has been defined as in figure 3, whereas each interval

denotes a specific event in the operation theatre. Hence, stimulus A mimics the response to intubation; B represents surgical incision followed by a period of no surgical stimulation (i.e. waiting for pathology result); C represents an abrupt stimulus after a period of low level stimulation; D shows onset of a continuous normal surgical stimulation; E,F, and G simulate short-lasting, larger stimulation within the surgical period; and H simulates the withdrawal of stimulation during the closing period.

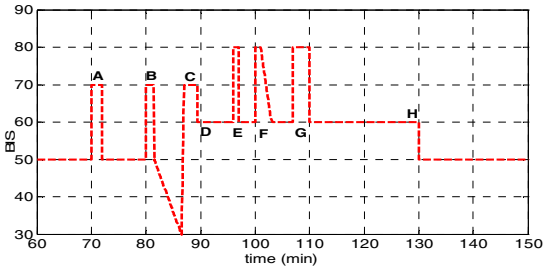

Fig. 3 The artificially generated disturbance signal

IV. Results

A. Induction Phase

Ideally, the induction of the patient in an operational DOA is required to be done as soon as possible, such that few time is lost before the surgeon can start. It is therefore desirable that the patient reaches the BIS=50 target and remains within the target value without much undershoot, i.e. values below BIS=30 should be avoided. A predictive controller can be either i) tuned such that the control effort is very significant, thus the response will be fast, at the cost of undershoot values; either ii) tuned in a conservative manner, such that the response is smooth but slow. This is achieved by tuning the value of the N_2 parameter (i.e. the prediction horizon). Figures 4 and 6 depict the results for prediction horizon of N_2=35 and N_2=12, respectively. Since our pool of patients varies significantly in the degree of sensitivity to Propofol according to the nonlinear relation from (3), it is clear that to obtain a good result for the entire set of patients, one must have a conservative controller, which brings smoothly the C_e values to their optimal levels, as concluded from figures 5 and 7, respectively.

The corresponding IAE values for each patient for the induction phase with the aggressive and the conservative MPC strategies have the mean and standard deviation 198.14±84.68 respectively 163.41 ±49.19.

B. Maintenance Phase

During the maintenance phase, it is important that the controller rejects the disturbances as soon as possible,

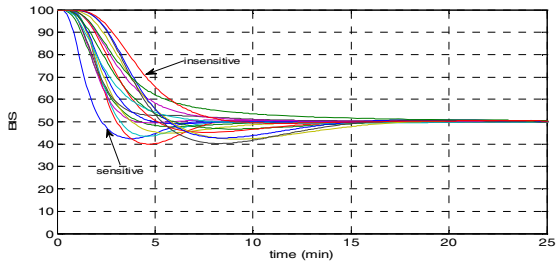

Fig. 4 Closed loop response of BIS during the induction phase with the conservative controller, for N_2=35

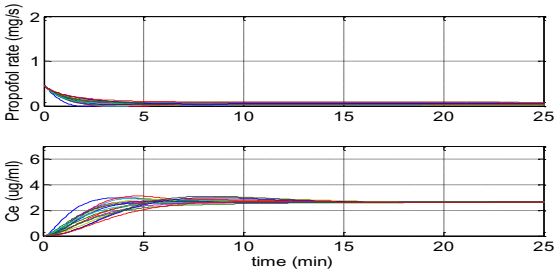

Fig. 5 Closed loop response of propofol rate and $C_e$during the induction phase with the conservative controller, for N_2=35

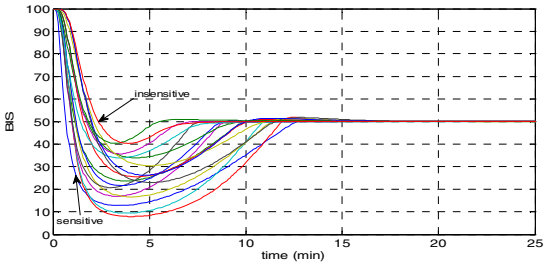

Fig. 6 Closed loop response of BIS during the induction phase with the fast/aggressive controller, for N_2=12

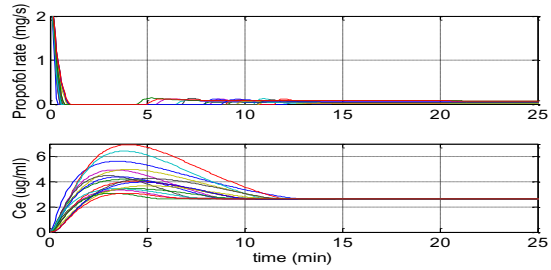

Fig. 7 Closed loop response of propofol rate and C_e during the induction phase with the aggressive controller, for N_2=12

keeping the patient within the BIS interval of 40 to 60 BIS values (thus around the BIS=50 value). The controller results for rejecting the disturbances defined in figure 3, are given in figures 8 and 10, for the two control designs, respectively. It can be observed that the aggressive controller

presented in figure 10 has a faster response to the disturbances but the undershoot is considerably greater than the case of the conservative controller. During this phase we can say that we obtain better performances if we use the conservative controller

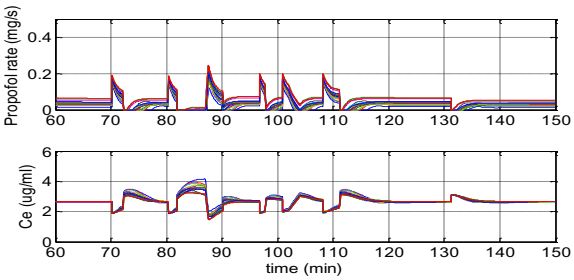

Fig. 8 Closed loop response of BIS during the maintenance phase with the conservative controller, for N_2=35

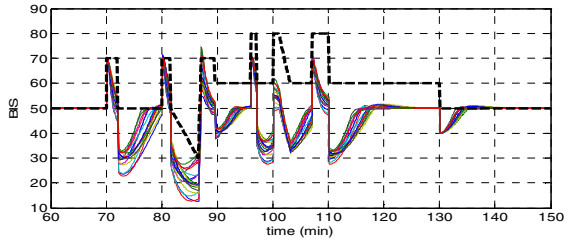

Fig. 9 Closed loop response of propofol rate and C_e during the maintenance phase with the conservative controller, for N_2=35

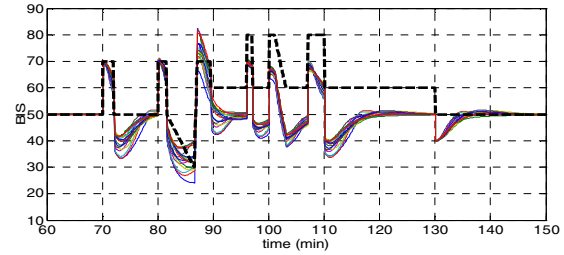

Fig. 10 Closed loop response of BIS during the maintenance phase with the aggressive controller, for N_2=12

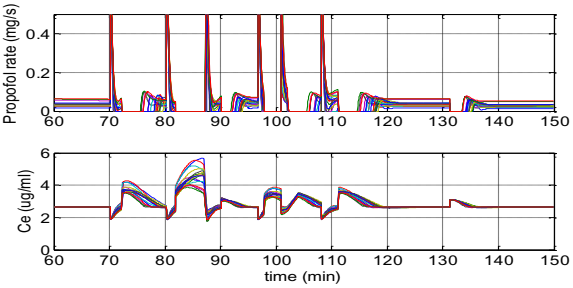

Fig. 11 Closed loop response of propofol rate and C_e during the maintenance phase with the aggressive controller, for N_2=12

V. Conclusions

In this paper, we discuss the robustness of a predictive anesthesia control strategy applied to a set of 17 virtually generated realistic patients. The patients pose significant variation in the sensitivity to the applied drug rates and the controller shows good performance despite strong inter-patient variability. The disturbance rejection tests are done on a realistic disturbance signal, capturing typical events from the operation theatre. Overall, the tuning of the predictive control algorithm in terms of the prediction horizon plays a crucial role in defining the controller speed in the closed loop paradigm.

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