MODEL BASED PREDICTIVE CONTROL OF DEPTH OF ANAESTHESIA

Shahab Abdulla
Faculty of Engineering and Surveying,
University of Southern Queensland
Shahab.Abdulla@usq.edu.au

Peng Wen
Faculty of Engineering and Surveying,
University of Southern Queensland
peng.wen@usq.edu.au

Zhou Zude
School of Information
Engineering, Wuhan
University of Technology
zudezhou@whut.edu.cn

Liu Quan
School of Information
Engineering, Wuhan
University of Technology
liuquan@whut.edu.cn

ABSTRACT

This study presents a new procedure to control the depth of anaesthesia by adjusting the amount of medication given to the patient to improve the recovery from anaesthesia. The procedure is based on model based predictive control technique, and the method is validated using measured clinical signals of BIS. Comparing to PID and internal model control, the proposed new method improves the performance of the closed-loop system in reference tracking, overall stability and uncertainties of the patient models and parameters.

KEYWORDS

Depth of Anaesthesia, Model Based Predictive Control

1. INTRODUCTION

Many surgical procedures would not be possible without the patient entering a state of unconsciousness. The essential features of a successful general anaesthesia, displayed by the patient, are a reversible loss of consciousness with a lack of movement, a lack of awareness, unresponsiveness to painful stimuli and a lack of recall of the surgical intervention. Inadequate general anaesthesia may lead to intra-operative awareness with recall (due to patient under dosage) or to prolonged recovery and an increased risk of postoperative complications for the patient (due to over dosage).The process of monitoring depth of anaesthesia and administration of a general anaesthetic during surgery is a closed-loop control system where the human is responsible for reasoning and action. Anaesthetists play the roles of controller and actuator by deciding on the amount of anaesthetic and when to administer it. On the other hand, the activity of monitoring is performed automatically by commercially available depth of anaesthesia monitors. Together they form a closed-loop control system. The proposed control systems are most often built around a well established BIS monitor, which is now standard equipment for anaesthesia monitoring. A well designed automatic control system can avoid both over and under-dosage of the drugs, which minimizes the drug consumption, intra-operative awareness and recovery times, thereby decreasing the cost of the surgery and the cost of the postoperative care.

Absalom et al. (2003) produced a closed-loop control system of anaesthesia that uses BIS as the control variable to automatically control the target blood concentration of Propofol (Target Controlled Infusion (TCI) system). The system was able to provide clinically sufficient anaesthesia in all patients, with enhanced accuracy of control. There was a tendency for more accurate control in those

patients in whom the control algorithm incorporated effect-site steering (Absalom and Kenny, 2003); (Engdahl et al., 1998). A method and an algorithm are proposed for controlling the effect site concentration using a TCI method. The method limits the peak plasma concentration, thereby slowing the start of anaesthetic drug effect but potentially improving side effects. Simulation is used to observe the delay in time to peak effect for five types of anaesthetic drug when the peak plasma concentration is limited by the algorithm; the control system was evaluated in 30 patient cases. This study clearly suggests the desirability of individual tuning of the controller parameters.

A method for an enhanced tuning of the PID controller parameters to the patient's individual dynamics was presented by Mendonca & Lago (Mendonca and Lago, 1998). Auditory Evoked Potentials (AEP) has been reported to accomplish many requirements for measurement of the level of anaesthesia. A development has been made to this system to obtain a single index which presents the morphology of the AEP and uses this index as the input signal for closed-loop anaesthesia during surgery in patients who did not receive neuromuscular blocking drugs (Kenny and Mantzaridis, 1999). A robust control of depth of anaesthesia was developed by Dumont et al. (2009) to design both robust and PID controllers based on fractional calculus to control the hypnotic state of anaesthesia with intravenous management of Propofol (Dumont et al., 2009). The objectives of these controllers are considered to compensate for the patient's inherent drug response variability, to accomplish good output disturbance rejection, and to achieve good tracking to set point response (Ejaz and Jiann-Shiou, 2004). The infusion and the drug effect are represented by the pharmacokinetic and pharmacodynamics models (Bressan et al., 2007).

Model Predictive Control (MPC) has been recognised, in process control, as a proven technology capable of dealing with a wide range of multivariable constrained control problems. Nevertheless, most industrial controllers are based on linear internal models, which limit their applicability.

This paper demonstrates the control of depth of anaesthesia using model based predictive control technique and compares its performance with PID and internal model control (IMC) approaches.

2. MODEL BASED PREDICTIVE CONTROL TECHNIQUE

A model based on a compartmental approach is used in this study. In each compartment, the drug concentration is homogeneous and there are exchanges between compartments. A three compartments model is used, in which the main compartment represents intravascular blood (blood within arteries and veins) and highly irrigated organs (such as heart, brain, liver and kidney). The two other compartments represent muscles, fat and other organs or tissues. The PK model consisting of 3-compartment is provided below and shown in Figure-1 (Dumont et al., 2009).

$$\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\\ \dot{c}_e\end{bmatrix} = \begin{bmatrix}-k_{10}-k_{12}-k_{13} & k_{21} & k_{31} & 0\\ k_{12} & -k_{21} & 0 & 0\\ k_{13} & 0 & -k_{31} & 0\\ k_{e0} & 0 & 0 & -k_{e0}\end{bmatrix}\begin{bmatrix}x_1\\ x_2\\ x_3\\ c_e\end{bmatrix} + \begin{bmatrix}B_2\\ 0\\ 0\\ 0\end{bmatrix}u \quad (1)$$

$$x(k+1) = Ax(k) + Bu(k) \quad (2)$$

$$y(k) = C_y\, x(k) \quad (3)$$

$$C_y = [C_2\ 0\ 0\ 0] \quad (4)$$

where x_1 represents the amount of drug in the central compartment, x_2 and x_3 denote the amount of the drug in compartments two and three, respectively. Also B_2 is equal to $\frac{10^4}{3600}$ and C_2 is equal to $\frac{1}{1\times v_1}$. The constants k_{ij} represent the transfer rate of the drug from the i^{th} compartment to the j^{th} compartment. The constant k_{10} is the rate of the drug metabolism and u is the infusion rate of the anaesthetic drug into the central compartment.

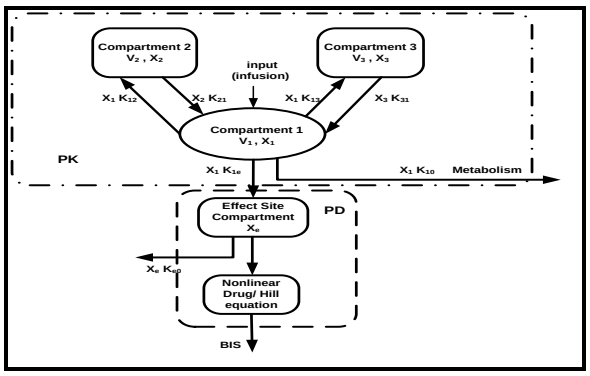

Figure 1 – Compartmental model of the patient

The pharmacodynamics is characterized by a low-pass filter related to the central compartment concentration C_p in blood:

$$C_e = \dot{x}_e = -k_{e0}x_e + k_{1e}x_1 \quad (5)$$

where k_{e0} and k_{1e} are constants and x_e is the amount of drug in the effect compartment and x_1 is the plasma Propofol and and Remifentanil concentrations.

$$C_e(s) = \frac{k_{e0}}{(s+k_{e0})} C_p(s) \quad (6)$$

where k_{e0} is the inverse of the effect-site compartment time constant and EC_{50} is the half-maximal effective concentration. γ is a steepness of the concentration response relation.

$$E(t) = E_o - E_{max}\left[\frac{{C_e}^{\gamma}}{EC_{50}^{\gamma}+{C_e}^{\gamma}}\right] \quad (7)$$

where E_0 represents the baseline value (conscious state without Propofol), which is typically set to 100; E_{max} denotes the maximum effect achieved by the drug infusion; EC_{50} is the drug concentration at half maximal effect and denotes the patient's sensitivity to the drug; and γ determines the steepness of the static nonlinearity.

2.1. MODEL PREDICTIVE CONTROL

The fundamental objective of MPC shown in Figure-2 is to determine the sequence of M future control policy (manipulated variable changes) so that the sequence of P predicted values (output variables) has minimal set-point tracking error (Shridhar and Cooper, 1997). The main purpose of the non-linear model predictive control is to find the future optimal drug infusion sequence in order to minimize a function based on a desired output trajectory over a prediction horizon to adjust the amount of medication given to improve recovery from anaesthesia (Yelneedi et al., 2009a). The cost function is the integral over the squares of the residuals between the models predicted outputs y and the set point values r over the prediction time.

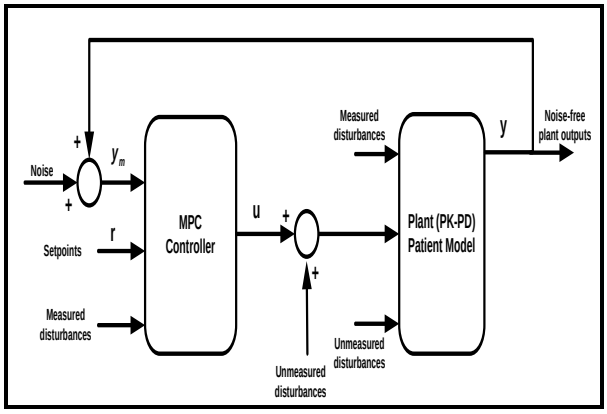

Figure 2 – Model predictive control scheme

where, r is the set-point of the target for the BIS, u is the controlled variable, the Propofol infusion rate ($u = r^{prop}$) given in [mL/h], y is the output, the DoA level given in [%], d is the disturbance ($d = c_e^{remi}$), the Remifentanil effect concentration given in [μg/mL], and $d = c_e^{prop}$ is the Propofol effect concentration given in [μg/mL].

Model Predictive Control (MPC) is currently the most accepted method for handling disturbances predicting and estimating changes (Jonker et al., 2005). MPC plays an important role in solving such complex problems. The main elements of the method are plant model, constraints and objective function, as shown in Figure-3. The objective function is evaluated and the selection of controller is repeated until the optimum is obtained (Bequette, 2007).

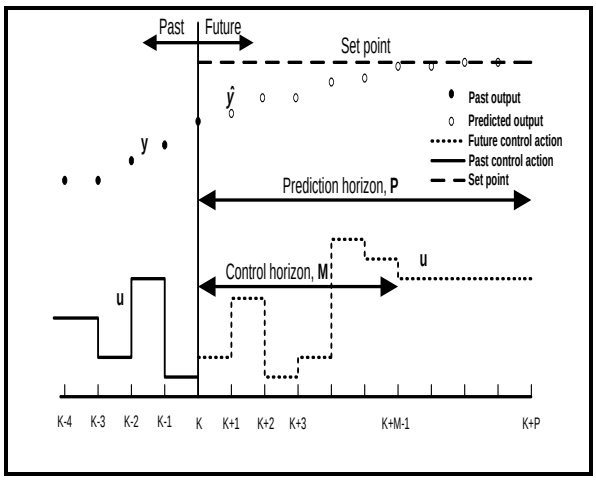

Figure 3 – The basic concept of model predictive control

The technique requires solution of optimization problem at every sampling time, other constraints on the drug infusion can be added, such as, that the drugs (propofol) rate are to remain constant during the last numbers of steps. A linear or quadratic cost functions will be used. Stability results are obtained on the same idea as made for linear systems. One or several of the following assumptions are made, terminal equality constraints, terminal cost function, terminal constraint set and dual mode control (infinite horizon): begin with MPC with a terminal constraint set, switch then to a stabilizing linear controller when the region of attraction of the linear controller is reached (Weber et al., 2004). Generally, an MPC algorithm consists of applying a control sequence that minimizes a multistage cost function. A typical formulation is

$$J = \sum_{i=k+1}^{k+P} e_i^T Q e_i + \sum_{i=k}^{k+M-1} \Delta u_i^T R \Delta u_i \quad (8)$$

Subject to:

$$u_{min} \le u_i \le u_{max} \quad (\text{for } i = k, k+1, k+2, \dots\dots, k+M-1)$$

$$u_{i-1} - \Delta u_{max} \le u_i \le u_{i-1} + \Delta u_{max} \quad (\text{for } i = k, k+1, k+2, \dots\dots, k+M-1)$$

where, M and P as the lengths of the prediction and control horizons, Q and R are the weighting matrices for both BIS and input rate respectively.

These Q and R can be used to tune the MPC controller to achieve the desired value between output performance and manipulated variable movement.

MPC controllers are based on an optimal control problem. Therefore, the weights used in the cost function should be determined. Another cost function for the MPC block in MATLAB (see equation (9)) has been used to improve the drug infusion during surgery (Cardoso and Lemos, 2008)

$$J = (Y-R)^T W_y^2 (Y-R) + \left(U - U^{desired}\right)^T W_u^2 \left(U - U^{desired}\right) + \Delta U^T W_{\Delta u}^2 \Delta U + \rho_\varepsilon \varepsilon^2 \quad (9)$$

where, W_u is a diagonal matrix representing the input weight, $W_{\Delta u}$ is a diagonal matrix representing the input rate weight, W_y is a diagonal matrix representing the output weight, $U = [u_t \cdots u_{t+M-1}]^T$ is the vector of values of the control signal over the control horizon, $U^{target} = [u_t^{target} \cdots u_{t+M-1}^{target}]^T$ is the vector of values of the desired control signal over the control horizon, $\Delta U = [\Delta u_t \cdots \Delta u_{t+M-1}]^T$ is the vector of values of the rate of the control signal over the control horizon, $Y = [y_{t+1} \cdots y_{t+P}]^T$ is the vector of values of the output over the prediction horizon, $R = [r_{t+1} \cdots r_{t+P}]^T$ is the vector of values of the reference over the prediction horizon, ρ_ε is the weight factor on the slack variable (used to penalize the violation of the constraints), and ε is the slack variable, a variable to turn the inequality into an equation, it allows the constraints to be violated by a certain amount.

2.2. CONSTRAINTS AND TIME HORIZON

The range of DoA signal is between 0 and 100% (initial signal is about 97.7%) and the Propofol infusion must be at a positive rate (a negative rate would mean that propofol was being taken from the patient). These constraints are summed as shown in Table 1.

Table 1 - Model predictive controller constraints

Variables	Minimum	Maximum
$u\,[\frac{mL}{h}]$	0	∞
$\frac{du}{dt}[\frac{mL}{hs}]$	$-\infty$	$+\infty$
DoA [%]	0	100

In reality, these are the basic constraints. The maximum drug infusion rate and the changes in the medication infusion rate are constrained by the apparatus and equipment, but these bounds are very high and are never reached in practice.

The prediction horizon P has been chosen based on open-loop settling time, whereas control horizon M is chosen based on the value between faster response (large value of M) and robustness (small value of M). Therefore, the chosen value for M is very small, compared to P. To reject the disturbances that are due to patient-model mismatch, the patient model is augmented by the output disturbance model, which is an integrator that is driven by white noise.

The MPC parameters are output (BIS) weight, Q = 1; input rate (Propofol) weight, R = 0.8; prediction (output) horizon, P = 30; and control (input) horizon, M =3. These parameters have been chosen by using direct search optimization for hypnosis regulation.

3. SIMULATION STUDY AND RESULTS

The main tuning parameters are the control and prediction horizons (M and P) and the weight applied to manipulated and control variables.

The prediction horizon determines the amount of predictions that are used in the optimisation calculations. Increasing the prediction horizon results in more conservative control action that has a stabilising effect, also increases the computional efforts (Yelneedi et al., 2009b). A very large predication horizon recommended only for a very good model and if feedback is limited.

The control horizon determines the number of future control actions that are calculated in the optimisation step to minimise the predicted errors. A large number for the control horizon, relatively to the prediction horizon, tends to too much control actions, but small value for control horizon leads to a robust controller.

The model predictive control simulation design shown in Figure-4, the patient model has been used to estimate the value of the output variable BIS. The difference between the measured BIS from the process model and the model output, serves as the feedback signal to the prediction part. With this model output and input variable, the prediction part estimates the future values of the output BIS. Base on the predicted BIS values, the MPC controller calculates the future input moves of which only first input move is implemented by the controller at current sampling instant.

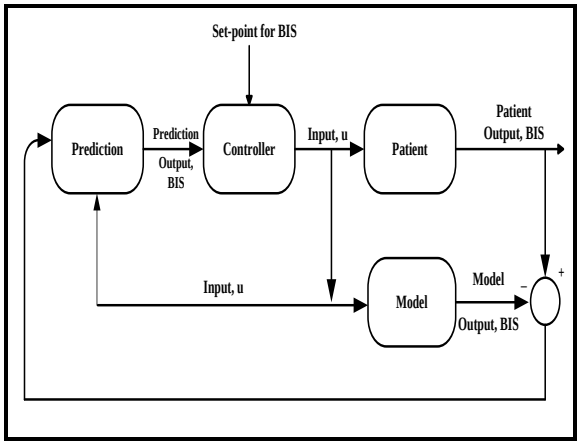

Figure 4 – The model predictive control simulation design

A Model Predictive Control system of Propofol and Remifentanil is constructed. The time that the BIS reaches the range of 50 ± 10, is called the settling time for the BIS during general anaesthesia. The specifications of the MPC system for the settling time range was between 5 and 10 mintues and the robutness was stable for all parameters obtained in the simulation results and is shown in Figure-5.

The target value of BIS is between 60 and 40. Figure-5 shows a simulation result for a subject with the nominal parameters. The MPC system can maintain BIS at the relevant target levels and the settling time is within ten minutes.

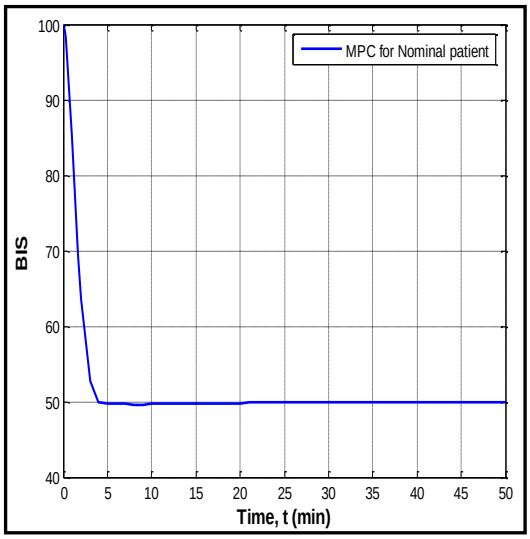

Figure 5 – The performance of the MPC for nominal patient

The predicted plasma Propofol concentration (C_p^{prop}) has to be between 0.5 µg/ml and 5 µg/ml because it is the clinically accepted range (Absalom et al., 2002) that is not measured but estimated using the nominal patient model.

The manipulated variables u (propofol infusion rate) is constrained between 0 and 20 mg/kg/hr (Furutani et al., 2005, Sawaguchi et al., 2008).

The tuning of the MPC design for the nominal patient's data for DoA parameters shown in Table 2. The MPC tuning parameters are M, and P, the input horizon and the prediction horizon respectively; Q and R, weighting coefficient for BIS and the weighting coefficient for the Propofol rate respectively. MPC controller performance for different tuning weights on the output variables and input variable rates for insensitive patients are shown in Figure-6.

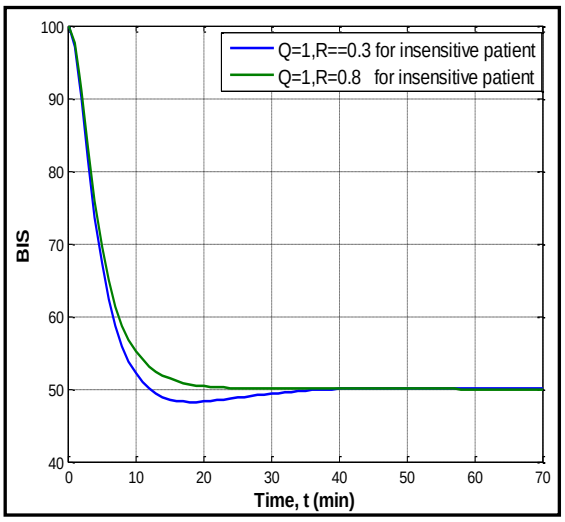

Figure 6 – MPC controller performance for different R and Q weights

Table 2 - Nominal patient's data for DoA parameters (MARSH et al., 1991, Minto et al., 1997)

Variable	Default value	Unit
v_c	0.228	[L/kg]
k_{10}	0.119	$[min^{-1}]$
k_{12}	0.112	$[min^{-1}]$
k_{13}	0.0419	$[min^{-1}]$
k_{21}	0.055	$[min^{-1}]$
k_{31}	0.0033	$[min^{-1}]$
k_{e0}	0.25	$[min^{-1}]$
EC_{50}^{remi}	11.20	[µg/mL]
EC_{50}^{prop}	2.65	[µg/mL]
E_0	97.7	[%]
γ	2.561	

The performance of MPC, IMC and PID for sensitive patients for the set-point tracking during the surgery period is shown in Figure-7. These three controllers (MPC, IMC and PID) are able to meet performance specifications in spite of the significant and reasonable variation in the model parameters such as inter-patient variability based on PK-PD model.

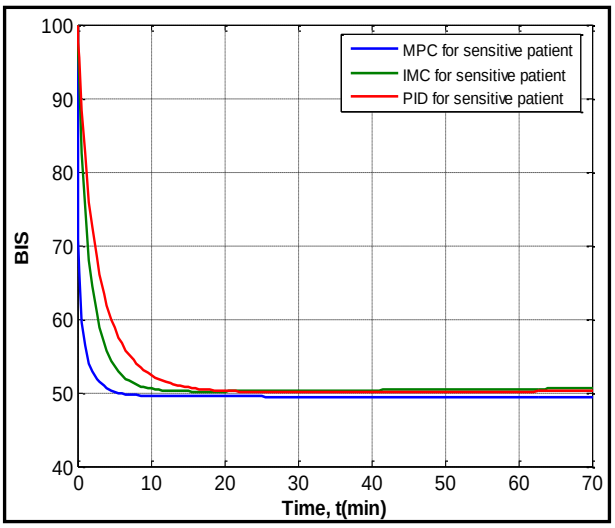

Figure 7 – The performance of MPC, IMC and PID controllers for sensitive patient

There is a variation in PK (based on age and weight) and PD (patient's sensitivity to the drug) model parameters.This assumption is based on the inter-patient and intra-patient variability (Schnider et al., 1999). The PK variation is about 25% of the model's parameters. In addition, simulation studies showed that the variability in PD parameters have more impact on BIS than the variability in PK parameters (Schüttler and Ihmsen, 2000).

The simulations results show that an insensitive patient requires relatively more Propofol and Remifentanil dosages and responds slowly to those drugs (as shown in Figure 8 for four different insensitive patients from Table 3).

Based on the PD parameters, changing the results shows that the higher EC_{50} indicates the need for more Propofol and Remifentanil drugs to get the same hypnosis and analgesia levels. Also higher γ (3.122) indicates higher non-linearity, and lower k_{e0} (0.239) represents slowness in response.

A sensitive patient requires less drug dosage to get the same hypnosis and analgesia levels. In PD parameters, lower EC_{50} indicates that less Propofol and Remifentanil are required to get the same level of hypnosis and analgesia. The lower amount of γ, represents weak non-linearity in the system response. Higher amount of k_{e0} indicates a quicker response.

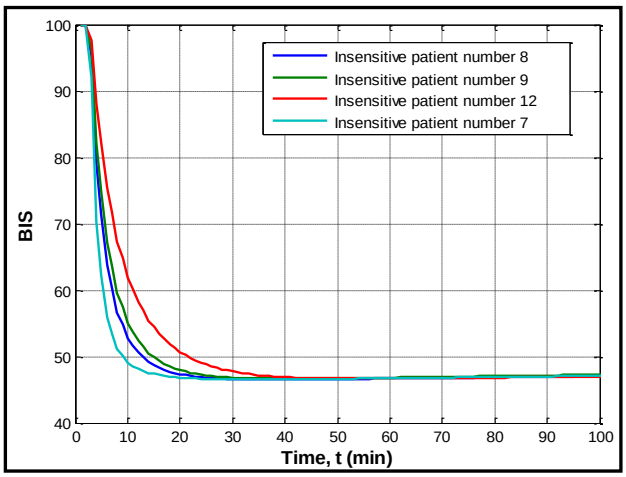

Figure 8 – The performance of MPC controllers for four insensitive patients

The performance of the three controllers (MPC, IMC and PID) is checked for the 12 patients, the insensitive, nominal and sensitive patients.

Table 3 - Patient PK-PD parameters for Remifentanil drug used in this study (Niño et al., 2009)

Patient	k_{10}	k_{12}	k_{21}	k_{13}	k_{31}	EC_{50}	k_{e0}	γ
1 (sensitive)	0.38175	0.2715	0.24375	0.00975	0.0175	7.840	0.6708	1.757
2	0.50900	0.3620	0.24375	0.01625	0.0105	7.840	0.6708	1.757
3	0.63625	0.2715	0.24375	0.01300	0.0140	7.840	0.6708	1.757
4	0.63625	0.2715	0.24375	0.01300	0.0140	7.840	0.6708	1.757
5	0.63625	0.2715	0.24375	0.01300	0.0140	7.840	0.6708	1.757
6 (Nominal)	0.50900	0.3620	0.19500	0.01300	0.0140	11.20	0.5160	2.510
7	0.50900	0.3620	0.19500	0.01300	0.0140	11.20	0.5160	2.510
8	0.50900	0.3620	0.14625	0.00975	0.0140	14.56	0.5160	1.757
9	0.63625	0.2715	0.14625	0.01625	0.0175	11.20	0.5160	1.757
10	0.38175	0.3620	0.19500	0.00975	0.0105	11.20	0.3612	1.757
11	0.50900	0.2715	0.14625	0.00975	0.0105	14.56	0.3612	2.510
12 (Insensitive)	0.63625	0.4525	0.14625	0.01625	0.0105	14.56	0.3612	3.263

The Simulink model structure can be seen in Figure-9.

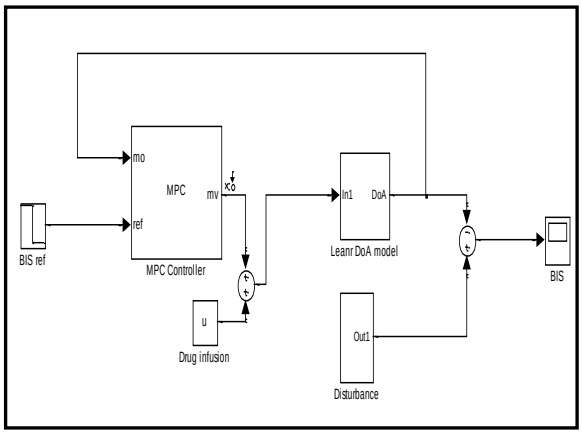

Figure 8 – The Simulink model structure

4. CONCLUSIONS

In this paper, a model predictive control strategy has been developed for automatic regulation of hypnosis and analgesia using BIS as controlled variables. The controllers were designed based on a nominal patient model, and then tested for their effectiveness, ability and robustness on 12 patient parameters covering sensitive to insensitive patients and operating conditions by the use of Simulink simulation.

The new models and control algorithms developed in this project is immediately useful in the development of new DoA control systems that have potential to greatly improve the comfort of patients, reduce the medical cost and avoid intraoperative awareness and all its consequences.

The results show that the MPC controller is capable of improving Propofol and Remifentanil inductions by 20 to 25% compared to PID controller, 8 to 10% compared to The IMC, and better robustness in set-point tracking and disturbance rejection when implemented on different patient parameters. In addition, the MPC control scheme is easier to design and does not need any complicated mathematical calculations.

5. REFERENCES

ABSALOM, A. R. & KENNY, G. N. C. 2003. Closed-loop control of propofol anaesthesia using bispectral indexTM: performance assessment in patients receiving computer-controlled propofol and manually controlled remifentanil infusions for minor surgery{dagger}. *Br. J. Anaesth.*, 90**,** 737-741.

ABSALOM, A. R., SUTCLIFFE, N. & KENNY, G. N. 2002. Closed-loop Control of Anesthesia Using Bispectral Index: Performance Assessment in Patients Undergoing Major Orthopedic Surgery under Combined General and Regional Anesthesia. *Anesthesiology*, 96**,** 67-73.

BEQUETTE, B. W. 2007. Non-Linear Model Predictive Control: A Personal Retrospective. *The Canadian Journal of Chemical Engineering,* 85**,** 408-415.

BRESSAN, N., CASTRO, A., BRAS, S., RIBEIROT, L., FERREIRA, D. A., SILVA, A., ANTUNES, L. & NUNES, C. S. Year. Modelling the dynamics of depth of anaesthesia: Cerebral state index in dogs. *In:* Control & Automation, 2007. MED '07. Mediterranean Conference on, 2007. 1-5.

CARDOSO, N. & LEMOS, J. M. Year. Model Predictive control of Depth of Anaesthesia: Guidelines for controller configuration. *In:* Engineering in Medicine and Biology Society, 2008. EMBS 2008. 30th Annual International Conference of the IEEE, 2008. 5822-5825.

DUMONT, G. A., MARTINEZ, A. & ANSERMINO, M. J. 2009. Robust control of depth of anesthesia. *International Journal of Adaptive Control and Signal Processing,* 23**,** 435-454.

EJAZ, K. & JIANN-SHIOU, Y. Year. Controlling depth of anesthesia using PID tuning: a comparative model-based study. *In:* Control Applications, 2004. Proceedings of the 2004 IEEE International Conference on, 2004. 580-585 Vol.1.

ENGDAHL, O., ABRAHAMS, M., BJORNSSON, A., VEGFORS, M., NORLANDER, B., AHLNER, J. & EINTREI, C. 1998. Cerebrospinal fluid concentrations of propofol during anaesthesia in humans

Product Information, Diprivan(R), propofol. *Br J Anaesth,* 81**,** 957 - 959.

FURUTANI, E., SAWAGUCHI, Y., SHIRAKAMI, G., ARAKI, M. & FUKUDA, K. Year. A hypnosis control system using a model predictive controller with online identification of individual parameters. *In:* Control Applications, 2005. CCA 2005. Proceedings of 2005 IEEE Conference on, 28-31 Aug. 2005 2005. 154-159.

JONKER, D. M., VISSER, S. A. G., VAN DER GRAAF, P. H., VOSKUYL, R. A. & DANHOF, M. 2005. Towards a mechanism-based analysis of pharmacodynamic drug-drug interactions in vivo. *Pharmacology & Therapeutics,* 106**,** 1-18.

KENNY, G. N. C. & MANTZARIDIS, H. 1999. Closed-loop control of propofol anaesthesia. *Br. J. Anaesth.,* 83**,** 223-228.

MARSH, B., WHITE, M., MORTON, N. & KENNY, G. N. C. 1991. PHARMACOKINETIC MODEL DRIVEN INFUSION OF PROPOFOL IN CHILDREN. *British Journal of Anaesthesia,* 67**,** 41-48.

MENDONCA, T. & LAGO, P. 1998. PID control strategies for the automatic control of neuromuscular blockade. *Control Engineering Practice,* 6**,** 1225-1231.

MINTO, C. F., SCHNIDER, T. W. & SHAFER, S. L. 1997. Pharmacokinetics and Pharmacodynamics of Remifentanil: II. Model Application. *Anesthesiology,* 86**,** 24-33.

MUNSON, E. S. & BOWERS, D. L. 1967. Effects of Hyperventilation on the Rate of Cerebral Anesthetic Equilibration: Calculations Using a Mathematical Model. *Anesthesiology,* 28**,** 377-381.

NIÑO, J., KEYSER, R. D., SYAFIIE, S., IONESCU, C. & STRUYS, M. 2009. EPSAC-controlled anesthesia with online gain adaptation. *International Journal of Adaptive Control and Signal Processing,* 23**,** 455-471.

SAWAGUCHI, Y., FURUTANI, E., SHIRAKAMI, G., ARAKI, M. & FUKUDA, K. 2008. A Model-Predictive Hypnosis Control System Under Total Intravenous Anesthesia. *Biomedical Engineering, IEEE Transactions on,* 55**,** 874-887.

SCHNIDER, T. W., MINTO, C. F., SHAFER, S. L., GAMBUS, P. L., ANDRESEN, C., GOODALE, D. B. & YOUNGS, E. J. 1999. The Influence of Age on Propofol Pharmacodynamics. *Anesthesiology,* 90**,** 1502-1516.

SCHÜTTLER, J. & IHMSEN, H. 2000. Population Pharmacokinetics of Propofol: A Multicenter Study. *Anesthesiology,* 92**,** 727-738.

SHRIDHAR, R. & COOPER, D. J. 1997. A tuning strategy for unconstrained SISO model predictive control. *Industrial & Engineering Chemistry Research,* 36**,** 729-746.

WEBER, F., BEIN, T., HOBBHAHN, J. & TAEGER, K. 2004. Evaluation of the Alaris Auditory Evoked Potential Index as an Indicator of Anesthetic Depth in Preschool Children during Induction of Anesthesia with Sevoflurane and Remifentanil. *Anesthesiology,* 101**,** 294-298.

YELNEEDI, S., LAKSHMINARAYANAN, S. & RANGAIAH, G. P. 2009a. A comparative study of three advanced controllers for the regulation of hypnosis. *Journal of Process Control,* 19**,** 1458-1469.

YELNEEDI, S., SAMAVEDHAM, L. & RANGAIAH, G. P. 2009b. Advanced Control Strategies for the Regulation of Hypnosis with Propofol. *Industrial & Engineering Chemistry Research,* 48**,** 3880-3897.