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International Journal of Current Research
Vol. 5, Issue, 10, pp.3133-3139, October, 2013

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

PERFORMANCE ANALYSIS OF NEURAL NETWORK BASED CONTROL OF HYPNOSIS AND ANALGESIA DURING ANESTHESIA BY EMPLOYING A PHARMACOKINETIC-PHARMACODYNAMIC MODEL

***Vinoth, N., Dr. Krishnan, J. and Malathi, R.**

Department of Electronics and Instrumentation Engineering, Annamalai University, Annamalainagar-608002, Tamilnadu, India

ARTICLE INFO

Article History:
Received 07th July, 2013
Received in revised form
20th August, 2013
Accepted 15th September, 2013
Published online 23rd October, 2013

Key words:
Isoflurane,
BIS,
MAP,
Anesthesia,
Analgesia, Hypnosis.

ABSTRACT

Monitoring and controlling the hypnosis and arterial pressure during a surgery is really vital since in excess of dosing and below dosing can be hazardous for the patients. Anesthesia drugs have impact on multiple results of an anesthesia patient. Automation of anesthesia is very useful as it will provide more time and flexibility to anesthesiologists to focus on critical issues that may arise during the surgery. Furthermore patient safety and cost reduction. Anesthetics are administered to regulate hypnosis and analgesia, respectively in the patient during the surgery. Most distinctive measures include Bispectral index (BIS), mean arterial pressure (MAP) and in general, BIS and MAP as the indirect measurements of hypnosis and analgesia, respectively. Isoflurane is given as the input to the Pharmocokinetic-pharmacodynamic model (PK-PD), from the model BIS and MAP were taken as output. In this work, a neural network based internal model controller (NN-IMC) is proposed by regulating the level of hypnosis and pressure. Performance of proposed approach is evaluated with conventional Proportional-Integral (PI) controller. Simulation results show that proposed NN-IMC outperforms conventional PI controller.

INTRODUCTION

The word anesthesia originates from the Greek word "aesthesia", which is found from the literatures and it means ability to sense and the prefix "an" for negation. Therefore, it means no ability to sense or a state of being unable to feel anything. Anesthesia can be defined as the lack of reaction and recall to noxious stimuli (Kaplan, 2002). The main goals of the anesthetist during general anesthesia are to provide hypnosis, analgesia, skeletal muscle relaxation and also to maintain the essential functions of the patient. Hypnosis illustrates a state of anesthesia which is not only related to unconsciousness of the patient but also to the disability of the patient to recall. The disability to recall is meticulously important as an awakening patient, might not feel pain and be aware of the operation procedures but cannot "converse" this to the medical team. The anesthesiologist must guarantee hypnosis and analgesia. Hypnosis, referred to as depth of anesthesia, is a general term specifying unconsciousness and absence of postoperative recall of events. Analgesia explains the disability of the patient to recognize pain. Pain cannot be directly measured. Clinically arterial blood pressure is often employed as an indirect sign of the pain (Bailey *et al*., 2005). Generally, anesthesiologists use BIS (level of hypnosis, a dimensionless number) and MAP as the indirect measurements of hypnosis and analgesia, respectively. During the surgery MAP should be observed and retained within the desired ranges. The MAP is maintained by the anesthesiologist by periodically infusing anesthetic drugs (Simpson and Popat, 2002).

Hypnosis is provided by management of hypnotic agents, which is an inhalable drug like Isoflurane (Gentilini *et al*., 2001). Isoflurane induce a decrease in MAP when administered to healthy subjects. Hence, Isoflurane gas is widely used in the anesthesia process. Automation of anesthesia is greatly helpful as it will provide additional time and flexibility to anesthesiologists to spotlight on significant issues that may occur for the duration of the surgery. Automation of drug delivery avoids both over dosages and under dosages. Moreover the drug delivery is based on the patient's response. This leads to minimum drug consumption, less intra operative awareness and shorter healing times, thereby decreasing the expenditure of surgery and also the expenditure of postoperative care. On the whole, this improves the patient's rehabilitation and safety during and after the surgery (Absalom *et al*., 2002). Earlier modeling, diagnosis, and controlling anesthesia focus on a single drug single output (Sartori *et al*., 2005), (Eisenach, 1999), (Furutani *et al*., 2005) and (Linkens, 1992). For a complete anesthesia management, it becomes essential that the impact of anesthesia drugs on multiple outcomes be taken into consideration. A various model and control strategies have are done for automation of

Corresponding author: Vinoth, N.,
Department of Electronics and Instrumentation Engineering, Annamalai University, Annamalainagar-608002, Tamilnadu, India

anesthesia (Gopinath, *et al*., 1995), (Rao, *et al*., 2001), (Zwart, *et al*., 1972) & (Simanski *et al*., 2008). (Gentilini *et al*., a,b, (2001)). [15] proposed a model for the control of MAP and BIS with Isoflurane. In this work, a five compartment model is proposed, which allows the simultaneous regulation of MAP as well as BIS. The proposed pharmacokinetics-pharmacodynamics (PK-PD) model has features as follows; PK which describes the uptake and distribution of the drugs, PD which is concerned with the effect of the drugs on the vital functions. The Isoflurane drug simultaneously controls the MAP and BIS. The paper is organized as follows: in section 2, review of PK-PD model is presented. Section 3 will review the control algorithm of NN-IMC, the result of the simulations is proposed in the subsequent sections and the conclusions are presented.

Mathematical modeling in anesthesia

The PK model is described by one central compartment and one or more peripheral compartments, which are linked to the central compartment. The PD model is described by an additional dynamic compartment, the effect site compartment and a static dose effect. The five compartment model, which is represented in this work as 'i'(where 'i' takes the value in the range of 2 to 5) comprising of Lungs, Liver, Muscles, other organs and fat tissues shown in Figure 1 (Sreenivas, *et al*. (2008)).

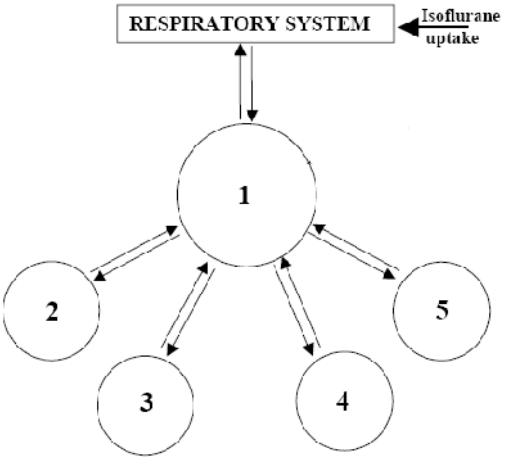

Figure.1. PK-PD Compartment model

The breathing system is approximated as a well-stirred tank (Gentilin *et al*., 2001). The relation between inspired anesthetic drug concentration C_{insp} (g/mL) to the fresh anesthetic gas concentration C_{in} (vol. g/mL) and parameters of the breathing system are given by the following equation

$$\frac{dC_{insp}}{dt} = \frac{(Q_{in}C_{in} - (Q_{in} - \Delta Q)C_{insp} - f_R(V_T - \Delta))}{V} \quad (1)$$

C_{out} is the concentration of isoflurane in the outlet stream (g/mL), Q_{in} is the inlet flow rate (mL/min), ΔQ are the losses (mL/min), V is the volume of the respiratory system (mL), f_R is the respiratory frequency (min^{-1}), V_T is the tidal volume (mL) and Δ is the physiological dead space (mL).

Pharmacokinetic model

The PK model for distribution of drug is described by a mass balance between the five compartments which are attached to the central compartment. The resulting mass balance for isoflurane in the central compartment is given in equation 2.

$$\frac{dC_1}{dt} = \sum_{2}^{5}\left(\frac{Q_1}{V_1}\left(\frac{C_i}{R_i} - C_1\right)\right) + \frac{f_R(V_T - \Delta)(C_{insp} - C_1)}{V_1} \quad (2)$$

Where C_i is the concentration of the drug in compartment i (g/mL), R_i is the partition coefficient between blood and tissues in compartment i, Q_i is the blood flow in compartment i (mL/min). Elimination of isoflurane by exhalation and metabolism in liver, the 2nd compartment, is given by (3)

$$\frac{dC_2}{dt} = \frac{Q_2}{V_2}\left(C_1 - \frac{C_2}{R_2}\right) - k_{20}C_2 \quad (3)$$

Where k_{20} is the rate of elimination of isoflurane in the 2nd compartment (min^{-1}).

For all the remaining compartments (except second compartment), the corresponding mass balance is given by (4) for i takes value from 3 to 5. C_i is the concentration of i^{th} compartment (g/ml).

$$\frac{dC_i}{dt} = \frac{Q_i}{V_i}\left(C_1 - \frac{C_i}{R_i}\right) \quad (4)$$

Pharmacodynamic model

A PD model is required to relate the consequence of drug on the hypnotic level (BIS) and Analgesia (MAP). The PK model is attached to an effect-site compartment model which signifies the time lag between the delivery of drug and its effect on BIS which is given by the nonlinear Hill equation (Beck, *et al*., 2007). The effect-site compartment accounts for the equilibration time between end tidal concentration and concentration of drug in the central nervous system. The effect-site concentration and end tidal concentration are related by a first-order lag given by (5)

$$\frac{dC_e}{dt} = k_{e0}(C_1 - C_e) \quad (5)$$

Where C_e is the concentration of isoflurane in the effect compartment (g/mL), and k_{e0} is the equilibration constant (min^{-1}).

The action of isoflurane on BIS (Sreenivas, *et al*. (2008)) can be expressed as follows

$$\Delta BIS = \Delta BIS_{MAX}\frac{C_e^{\gamma}}{C_e^{\gamma} + EC_{50}^{\gamma}} \quad (6)$$

$$\Delta BIS = BIS - BIS_0 \quad (7)$$

$$\Delta BIS_{MAX} = BIS_{MAX} - BIS_0 \quad (8)$$

Where EC_{50} is the concentration of drug at half-maximal effect and represents the patient's sensitivity to the drug, and γ is a dimensionless parameter that determines the degree of nonlinearity. BIS has the range between 0 and 100, where $BIS_0 = 100$ denotes a fully conscious state and $BIS_{MAX} = 0$ denotes deep coma. By substituting equations (6) and (7) into equation (8),

$$BIS = 100 - 100\frac{C_e^{\gamma}}{C_e^{\gamma} + EC_{50}^{\gamma}} \quad (9)$$

The nominal values of the parameters k_{e0} = 0.3853 min−1, E_{C50} = 0.7478 vol. % and γ = 1.534 are taken from (Sreenivas, Y *et al*. (2008)).

The action of isoflurane on MAP (Pinky Dua., *et al*., 2005) can be expressed as follows

$$MAP = \frac{Q_1}{\sum_{i=2}^{5}\left(g_{i,0}(1 + b_i c_i)\right)} \quad (10)$$

Where, $g_{i,0}$ are the baseline conductivities (mL/(min mmHg)) and b_i are the variation coefficients of conductivity (mL/g).
The nominal values of the parameters used in this model are referred from (Pinky Dua., *et al*., 2005). These parameter values are based upon the values reported in the literature for the various organs, within a compartment.

Neural Network based IMC

The way in which the neurons of a neural network are organised is intimately linked with the learning algorithm used to train the network. Learning algorithm used in the design of the neural networks as being structured. Feed forward neural network distinguishes itself by the presence of one or more hidden layers whose computation nodes are correspondingly called hidden neurons. The function of the hidden neurons is to intervene between the external inputs and the network output in some useful manner. Artificial neural networks (ANN) are trained by adjusting these input weights, so that the calculated outputs may be approximated by the desired values. The output from a given neuron is calculated by applying a transfer function to a weighted summation of its input to give an output, which can serve as input to other neurons as follows.

$$\alpha_{jk} = F_k\left(\sum_{i-1}^{k-1}\sum w_{ijk}\alpha_{i(k-1)} + \beta_{jk}\right) \quad (11)$$

The model fitting parameters w_{ijk} are the connection weights. The nonlinear activation transfer functions F_k. The training process requires a proper set of data i.e., input (I_1) and target output (t_i). During training the weights and biases of the network are iteratively adjusted to minimize the network performance function. The typical performance function that is used for training feed forward neural networks is the network Mean Squares Errors (MSE).

$$MSE = \frac{1}{N}\sum_{i=1}^{N}(e_i)^2 = \frac{1}{N}\sum_{i=1}^{N}(t_i - \alpha_i)^2 \quad (12)$$

There are many different types of neural networks, differing by their network topology and/or learning algorithm. In this paper the back propagation learning algorithm, which is a multilayer feed forward network with hidden layers between the input and output. The simplest implementation of back propagation learning is the network weights and biases updates in the direction of the negative gradient that the performance function decreases most rapidly. An iteration of this algorithm can be written as follows.

$$x_{k+1} = x_k - l_k g_k \quad (13)$$

There are various back propagation algorithms such as Scaled Conjugate Gradient (SCG), Levenberg-Marquardt (LM) and Resilient back Propagation (RP). Among these LM is the fastest training algorithm for networks (Narendra and Parthasarathy, 1990) of moderate size and it has the memory reduction feature to be used when the training set is large.

Generation of Input-Output data

By changing the infusion rate as random number sequence is given as input to the PK-PD as shown in Figure 2 and the corresponding output is obtained as shown in Figure 3,4 The identification data set, containing N = 1000 samples with sampling time of 15 sec.

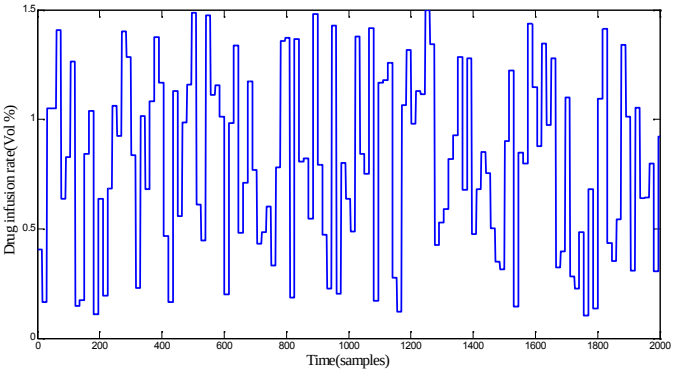

Figure 2. Random input to PK-PD model

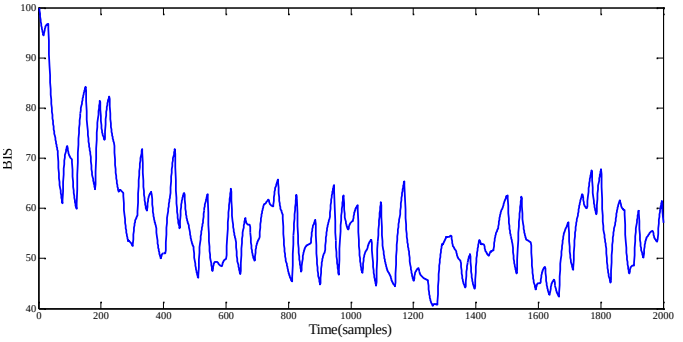

Figure 3. BIS response of PK-PD model

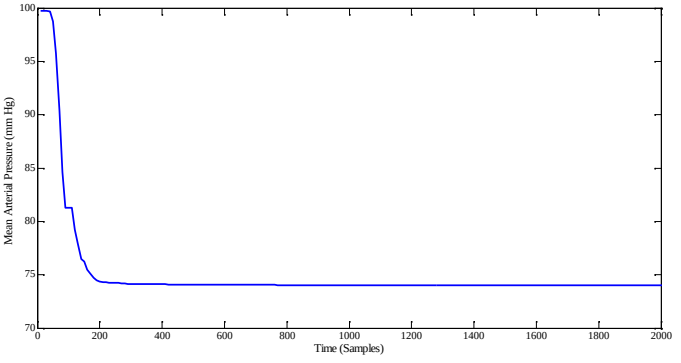

Figure 4. MAP response of PK-PD model

Forward Neural Model of PK-PD model

The neural network approach is trained to represent the forward dynamics of the PK-PD model. The network is trained

using delayed outputs and current input. The Activation function for the hidden layer is tansigmoidal, while for the output layer linear function is selected and they are bipolar in nature. The block diagram of forward neural network model is shown in Figure 5. The Levenberg Marquardt (LM) learning algorithm (Narendra and Parthasarathy, 1990) (Sivaraman and Arulselvi, 2011) does the correct choice of the weight.

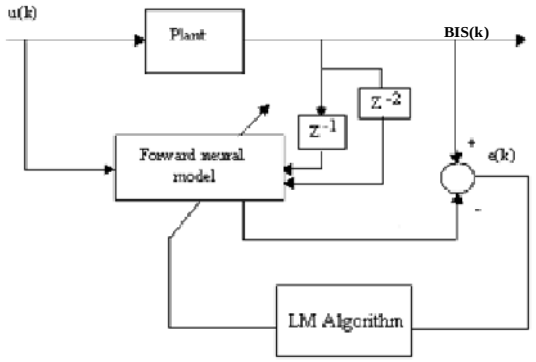

Figure 5. Block diagram of forward neural model

Training and Model validation of forward Neural Model

The data set used for training is sufficiently rich to ensure the stable operation, since no additional learning takes place after training. During training the NN learns the forward of the PK-PD dynamics by fitting the input-output data pairs. This is achieved by using the LM algorithm. The simulated forward model output is shown in Figure 6, 7. It is observed from Figure 6, 7 that forward model output exactly matches with output of the actual process. Hence, the neural network has the ability to model forward dynamics of the PK-PD model, which can be used for developing the model based controllers.

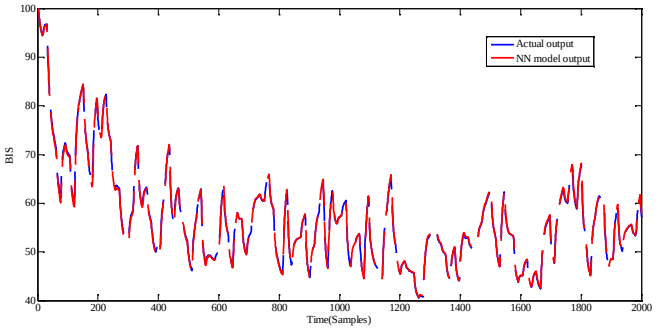

Figure 6. Response of forward neural model and Actual BIS output

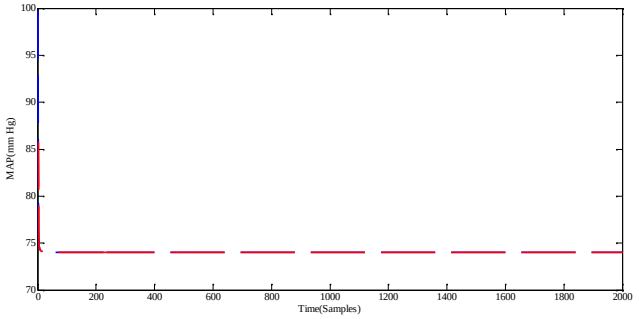

Figure.7. Response of forward neural model and Actual MAP output

Direct Inverse Neural Model of PK-PD model

The neural network approach is also trained to capture the inverse dynamics of the PK-PD model,. The network is trained using delayed sample of outputs and delayed input of PK-PD model. The Activation function for hidden layer and output layer are bipolar tansigmoidal and bipolar pure linear are used to give the desired output as BIS and MAP, which is input signal for the PK-PD model. The block diagram of direct inverse neural model is shown in Figure 8.

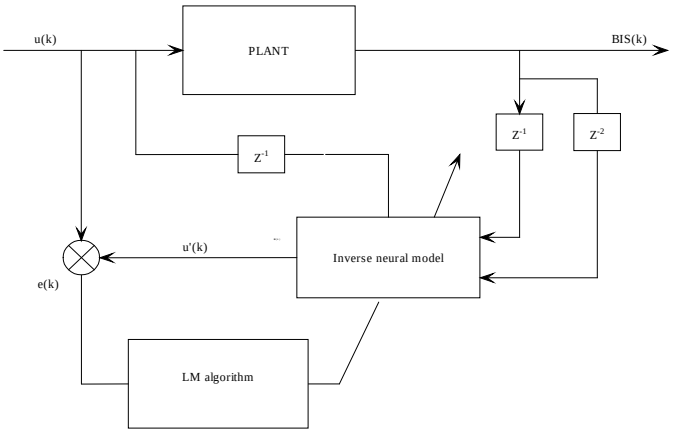

Figure 8. Block diagram of direct inverse neural model

Training and model validation of inverse neural model

During training the NN learns the inverse of the PK-PD model, by fitting the input-output data pairs. This is achieved by using the LM algorithm. It is clear from Figure.9 that the inverse model output exactly matches with input of the actual model. Hence the neural network has the ability to model inverse BIS and MAP, which can be used for developing model-based controllers.

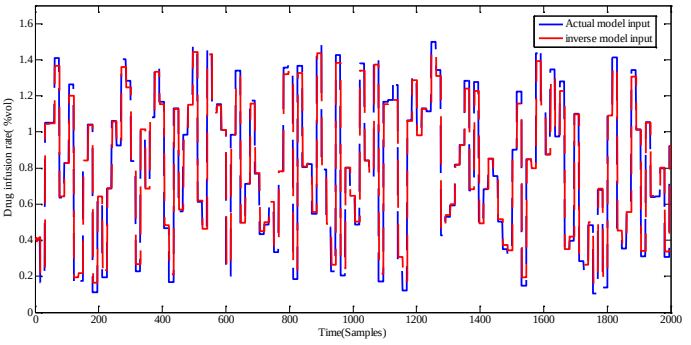

Figure 9. Response of inverse neural model and actual input of the model

Design of Direct Inverse Neuro Controller for PK-PD model

In the direct inverse control technique, the inverse model acts as the controller in cascade with the system under control, without any feedback. In this case the neural network, acting as the controller. In this control scheme the desired setpoint acts as the desired output which is fed to the network together with the past plant inputs and outputs to predict the desired current plant input. The direct inverse neural controller is shown in Figure.10.

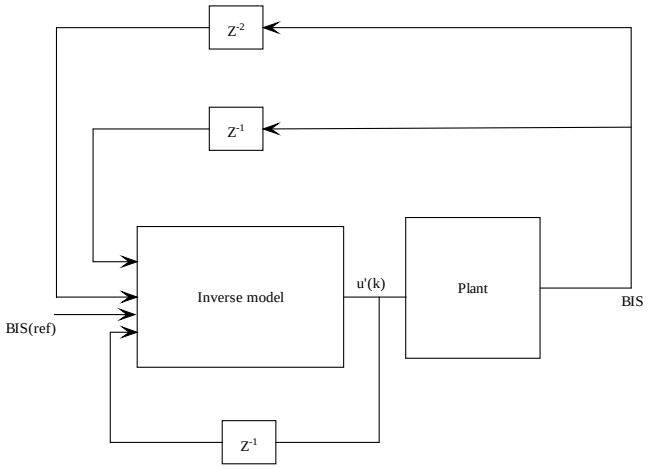

Figure 10. Block diagram of inverse neural model

Design of Neural Internal Model Controller

The Internal Model Control (IMC) philosophy relies on the Internal Model Principle, which states that control can be achieved only if the control system encapsulates, either implicitly or explicitly, some representation of the process to be controlled. In particular, if the control scheme has been developed based on an exact model of the process, then perfect control is theoretically possible. In practice, however, process-model mismatch is common; the process model may not be invertible and the system is often affected by unknown disturbances. The open loop control arrangement will not be able to maintain output at set point. Nevertheless, it forms the basis for the development of a control strategy that has the potential to achieve perfect control. This strategy is called as Internal Model Control. The neural internal model control approach (Hunt *et al*., 1992) is similar to the direct inverse control approach above except for two additions. First is the addition of the forward model placed in parallel with the plant, to cater for plant or model mismatches and second is that the error between the plant output and the neural net forward model is subtracted from the set point before being fed into the inverse model. The other data fed to the inverse model is similar to the direct method. A filter can be introduced prior to the controller in this approach to incorporate robustness in the feedback system, especially where it is difficult to get exact inverse models. The neural internal model controller is shown in Figure 11.

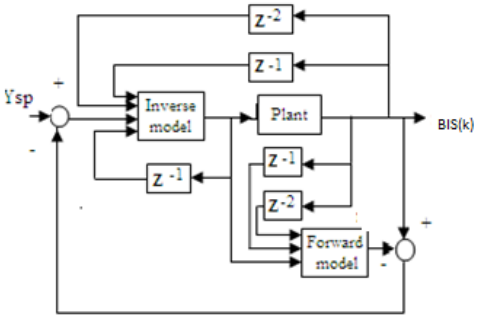

Figure 11. Block diagram of internal model control

SIMULATION RESULTS AND DISCUSSIONS

The nominal input range of BIS is in the range 0 to 5% volume of isoflurane, the BIS range for the anesthetic state is of the range 40 to 65 and the range of MAP is between 60 to 150 mmHg. Open loop simulation of the model was done to observe the effect of isoflurane on MAP and BIS. Figure 12, 13 shows the open loop response of the PK-PD model.

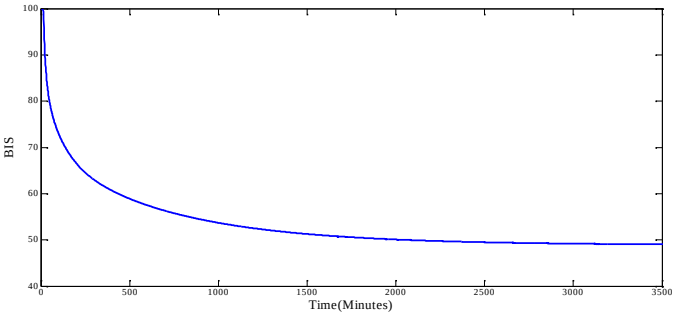

Figure 12. Open loop response of BIS

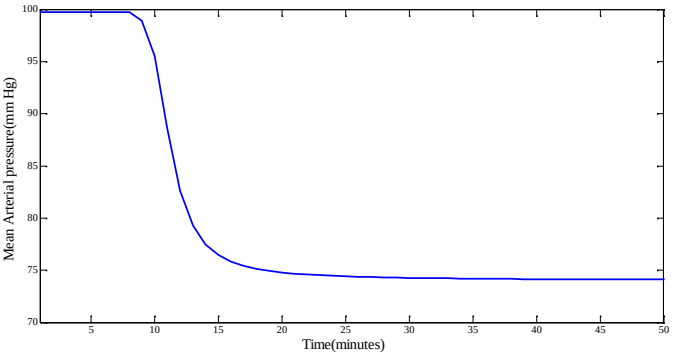

Figure 13. Open loop response of MAP.

From the output it can be observed that BIS requires long duration to attain the steady state. With the step change of 0.8% volume of isoflurane leads to the nominal value of BIS is 49 and MAP is 74 mmHg. Figure 14, 15 shows the closed loop response of PK-PD model with PI controller implemented by pole placement method.

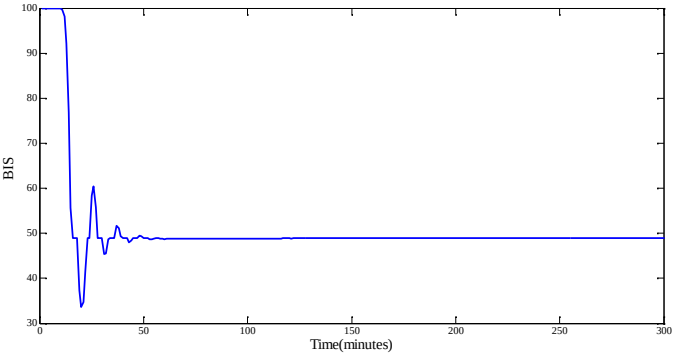

Figure 14.Closed loop response of BIS by PI controller

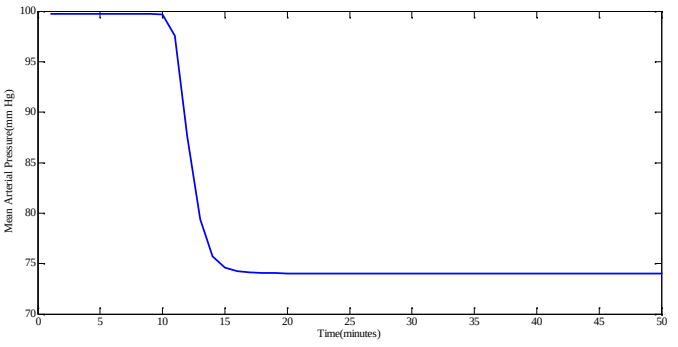

Figure 15. Closed loop response of MAP by PI controller

Figure 16, 17 shows the response of NN-IMC controller which seems to have faster settling time than that of PI controller, from this it can be concluded that amount of drug administrated in NN-IMC is less than the PI controller. By comparing PI and NN-IMC, from the PI controller output it is observed that it has over shoot and under shoot which is undesirable in surgical environment, which is not observed in NN-IMC. The performance criteria of PI and NN-IMC are measured using ISE and IAE are tabulated in Table 1.

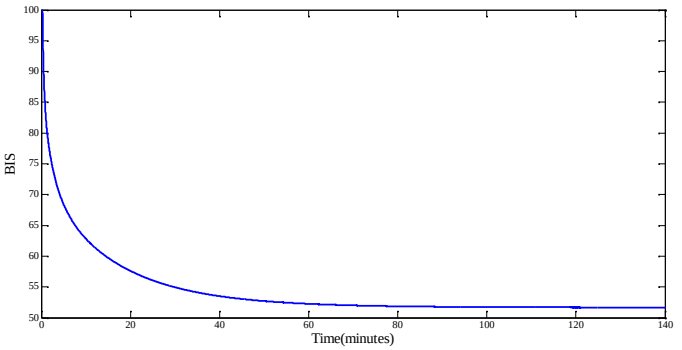

Figure 16. Closed loop response of BIS by NN-IMC controller

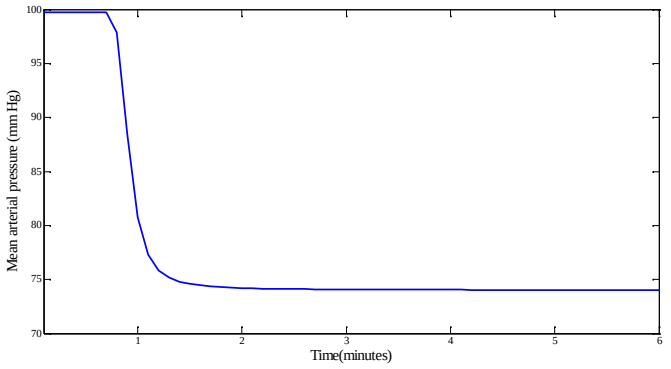

Figure 17. Closed loop response of MAP by NN-IMC controller

Table 1. performance measures of PI and NN-IMC

CONTROLLER	ISE(MAP)	IAE(MAP)	ISE(BIS)	IAE(BIS)
PI CONTROLLER	$9.63x10^4$	3103	2424	112
NN-IMC CONTROLLER	$5.151x10^4$	716	653	45

From the Table 1 it is observed that NN-IMC's ISE and IAE are lesser value than PI controller. From the above observations it is seen that NN-IMC outperforms the PI controller.

Conclusion

Automatic regulation of anesthesia can provide tighter control allowing anesthesiologist to focus on more critical issues which will result in less time spent by the patients in the post-operative care unit, reduction in the amount of drugs used and side-effects and above all a much safer platform for surgery under anesthesia. A compartmental model for anesthesia based upon the infusion of drugs for the simultaneous regulation of MAP and BIS of the patient has been presented. From the results it can be inferred that NN-IMC controller has enhanced performance on BIS and MAP simultaneously. During surgery the presence of noise and disturbances are inevitable, automation leads to controlling the BIS and MAP.

REFERENCES

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*(1), pp 67–73.

Bailey, J. M., & Haddad, W. M. 2005. "Drug dosing control in clinical pharmacology". *IEEE Control Systems Magazine*, *25*, vol2, pp35–51.

Beck, C., Lin, H.-H., & Bloom, M. 2007. "Modeling and control of anesthetic pharmacodynamics". In *Lecture Notes in Control and Information Sciences – Biology and Control Theory: Current Challenges*, Vol. 357, Springer-Verlag: Berlin, Heidelberg, pp. 263–289.

Eisenach, J.C., 1999. "Reports of Scientific Meetings - Workshop on Safe Feedback Control of Anesthetic Drug Delivery", *Anesthesilogy*, vol. 91, pp. 600-601.

Furutani, E., Y. Sawaquchi, and G. Shiralami *et al*. 2005. "A hypnosis control system using a model predictive controller with online identification of individual parameters", *IEEE control application conference*, pp. 154-159.

Gentilini, A., C.W. Frei, A.H. Glattfelder, M. Morari,T.J. Sieber, R. Wymann, T.W. Schnider andA.M. Zbinden. b, 2001". Multiasked closed-loop control in anesthesia". *IEEE Engineering in Medicine and Biology*, vol.20, pp39-53.

Gentilini, A., Rossoni-Gerosa, M., Frei, C. W., Wymann, R., Morari, M., Zbinden, A. M., & Schnider, T. W. a, 2001. "Modeling and closed-loop control of hypnosis by means of bispectral index (BIS) with isoflurane". *IEEE Transactions on BiomedicalEngineering*, *48*, vol 8, pp 874–889.

Gopinath R., B.W. Bequette, R.J. Roy and H.Kaufman. 1995. "Issues in the design of a multirate model-based controller for a nonlineardrug infusion system". *Biotech Prog*. vol. 11, pp318-332.

Hunt., K.J., D. Sbarbaro, R. Zbikowski and P.J. Gawthrop. 1992. "Neural Networks for control systems-a survey, *automatica*, Vol 28, pp 1083-1112.

Kaplan, A. J. 2002. "Cardiac Anesthesia". Philadelphia, PA: Saunders.

Linkens, D.A., 1992. "Adaptive and Intelligent Control in Anesthesia", *IEEE Control Systems Magazine*, vol. 12, pp. 6-11.

Narendra, K.S. and K. Parthasarathy 1990. "Identification and control of dynamic systems using neural networks, *IEEE Transactions on Neural Networks*, Vol.1, pp 4-27.

Pinky Dua, Vivek Dua & E.N. Pistikopoulos**.** 2005. "Model based drug delivery for anesthesia". In 16th Triennial World Congress, Prague, pp. 95–100.

Rao, R.R., C.C. Palerm, B. Aufderheide and B.W. Bequette. 2001. "Automated regulation of hemodynamic variables". *IEEE Engineering in Medicine and Biology*, vol.20, pp24-38.

Sartori, V., P.M. Schumacher, and M. Morari *et al*, 2005. "On-line estimation of propofol pharmacodynamic parameters", in 27th Annual International Conference of the Engineering in Medicine and Biology Society, pp. 74-77.

Simanski, O., R. Kaehler, A. Schubert, M. Janda, J. Bajorat, R. Hofmockel and B.P. Lampe 2008. "Automatic drug

delivery in anesthesia – the design of an anesthesia assistant system". Proceedings of the 17th World Congress The International Federation of Automatic Control Seoul, Korea, July 6-11.

Simpson, P.J. and M. Popat 2002. "Understanding Anaesthesia", 4th Edition, Butterworth Heinemann, Oxford.

Sreenivas, Y., Lakshminarayanan, S., & Rangaiah, G. P. 2008. "Advanced regulatory controller for automatic control of anesthesia". In *IFAC Proceedings*, Vol. 17, pp. 11636–11641.

Zwart, A.N., N.T. Smith and J.E.W. Beneken. 1972. "Multiple model approach to uptake and distribution of halothane: the use of an analog computer". *Computers and Biomedical research*, vol.5, pp228-238.

Sivaraman.E, Arulselvi.S (2011) "Neuro modeling and control strategies for a ph process". *International Journal of Engineering Science and Technology* 3 (1), 194-203.

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