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Research Article

MODEL-BASED APPROACH ON THE EFFECT OF ISOFLURANE AND CONTROL OF CRITICAL HEMODYNAMIC VARIABLES

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ABSTRACT

Monitoring and control of physiological variables during surgeries is a difficult task since the manual infusion of drugs leads to complications in patients. Anaesthesia is mainly used to maintain most the critical physiological parameters. Automatic control of these parameters will help the anaesthetist to focus on other issues that has to be taken care of. This paper presents about the closed loop control of anaesthesia drug that is used to maintain the safety limits of physiological variables such as hypnosis in terms of Bi-Spectral Index (BIS), analgesia in terms of Mean Arterial Pressure (MAP) and Heart Rate (HR). Here isoflurane is anaesthesia that is used as the medicine to administer the parameters. Pharmacokinetic (PK) and Pharmacodynamic (PD) modeling is carried out for isoflurane drug and control action is implemented based on the open loop response of the PK-PD model. The performance of the model is compared for Proportional-Integral (PI) controller and Neural Network Internal Model Control (NN-IMC) and the simulation results are obtained using MATLAB.

Keywords: Anaesthesia, Bi-Spectral Index, Heart Rate, hypnosis, Mean Arterial Pressure, physiological variables, simulation.

INTRODUCTION

Anaesthesia is defined as the state of losing conscious or sensation temporarily. The patient with the effect of anaesthesia is commonly referred as anaesthetized. Anaesthesia drugs are the medicines that are administered into patients to carry out any form of medical procedures [1,2]. The main objective of inducing anaesthesia is analgesia, hypnosis and muscle relaxation. Analgesia is the state when the patients are relieved from the severity of pain. Hypnosis is referred as the state of unconsciousness. When the anaesthesia is infused or inhaled by the patient, the hypnotic state is reached within a short span of time and it provides disability to recall the events [3-6]. Analgesia is insensibility to pain without the loss of consciousness which is measured in terms of Mean Arterial Pressure (MAP) since the pain cannot be measured directly. Hypnosis is the measure of the depth of anaesthetic agent which is measured in terms of Bi-Spectral Index (BIS). Heart Rate (HR) is usually determined using various complex factors [7]. In a normal resting human, heart rate remains normal. When a stress or a state of strain is enforced on the body usually heart rate increases. During surgery, there are variations in the heart rate. In order to maintain it, anaesthesia plays a vital role.

Isoflurane is a non-flammable liquid that are delivered via inhalation. They are usually delivered by anaesthetist using an anaesthetic mask, laryngeal mask airway or tracheal tube that is connected to an anaesthetic delivery unit [8]. Recovery from hypnotic state is rapid using isoflurane. The level of analgesia and hypnosis can be varied rapidly with isoflurane. As isoflurane is given through inhalation process, the respiration must be monitored periodically. When stress is given to the body (surgical procedure), it results in higher heart rate which in turn causes the rapid increase in blood pressure by administering the inspiration of isoflurane, the blood pressure decreases [9,10]. When over dosage of anaesthetic drug is given, it easily affects the brain and heart. Thus an effective and complete administration and controlled delivery of the anaesthesia is required for speedy recovery of the patients.

MATERIALS AND METHODS

Model Description

The mathematical modeling of the isoflurane is determined by pharmacokinetic and pharmacodynamic modeling as shown in Figure 1. Pharmacokinetic (PK) is the model developed by considering five compartments which includes one central compartment and four peripheral compartments [11-14]. The PK model deals with the uptake and distribution of drugs. The peripheral compartment includes lungs, liver, kidneys and other organs and fat tissues. The pharmacokinetic compartment modeling is exhibited with the equations (1)-(9).

The mass balance equation of the each compartment is derived as-

$$V_i \frac{dC_{i,j}}{dt} = Q_i \left(C_{ar,j} - \frac{C_{i,j}}{R_i} \right) - K_{i,j} C_{i,j} \quad (1)$$

Where V_i is the volume of the compartment
$C_{i,j}$ is the drug concentartion in the compartment
Q_i is the blood flow to the compartment

$K_{i,j}$ is the rate constant
$C_{ar,j}$ is the drug concentratioin in arteries
R_i is the partition oefficient between blood and tissues in the compartment
The flow rate of blood is expressed as-

$$Q_{i,out} = \frac{Q_{i,n}}{R_i}, Q_{i,n} = Q_i \quad (2)$$

Where $Q_{i,n}$ is the inlet flow rate of blood
$Q_{i,out}$ is the outlet flow rate of blood
Considering the concentration of the drug in arteries is equal to the concentration of drug in the outlet flows from central compartment, the equation is obtained as-

$$V_i \frac{dC_{i,j}}{dt} = Q_i \left(C_{1,j} - \frac{C_{i,j}}{R_i}\right) - K_{i,j} C_{i,j} \quad (3)$$

The inhalation process of isoflurane carried out through respiratory system is modeled as-

$$V \frac{dC_{inhale}}{dt} = Q_{in} C_{in} - (Q_{in} - \Delta Q) C_{inhale} - f_R (V_T - \delta)(C_{inhale} - C_O) \quad (4)$$

Where C_{inhale} is the concentration of the isoflurane inhaled by the patient $(\frac{g}{ml})$
C_{in} is the concentration of isoflurane in inlet stream $(\frac{g}{ml})$
C_O is the concentration of isoflurane in outlet stream $\left(\frac{g}{ml}\right)$
f_R is the frequency of respiration $(\frac{l}{min})$
V_T is the tidal volume (l)
V is the volume of respiratory system (l)
δ is the physiological dead space (ml)
Q_{in} is the inlet flow rate $(\frac{ml}{min})$
ΔQ are the losses $(\frac{ml}{min})$
Due to the elimination of isoflurane by exhalation and metabolism by liver, the peripheral compartment 2 is modeled as-

$$V_2 \frac{dC_2}{dt} = Q_2 \left(C_1 - \frac{C_2}{R_2}\right) - K_{20} C_2 V_2 \quad (5)$$

Where K_{20} is the rate of elimination of isoflurane in peripheral compartment 2.
The concentration of isoflurane in compartments 3, 4 and 5 are obtained as-

$$V_k \frac{dC_k}{dt} = Q_k \left(C_1 - \frac{C_k}{R_k}\right) \; for \; k = 3,4,5 \quad (6)$$

Pharmacodynamic modeling deals with the non-linear dynamics of BIS, MAP and HR to that of concentration of effect-site compartment. The effect-site compartment modeling with non-linearity is usually expressed in terms of Sigmoid Hill equation [15-19] as shown in equations (7)-(9).

$$BIS = Eff_{0,b} - Eff_{max,b} \left(\frac{C_e^\gamma}{C_e^\gamma + C_{50}^\gamma}\right) \quad (7)$$

$$MAP = Eff_{0,m} - Eff_{max,m} \left(\frac{C_e^\gamma}{C_e^\gamma + C_{50}^\gamma}\right) \quad (8)$$

$$HR = Eff_{0.h} + Eff_{max,h} \left(\frac{C_e^\gamma}{C_e^\gamma + C_{50}^\gamma}\right) \quad (9)$$

Where $Eff_{0,b,}$ $Eff_{0,m}$ and $Eff_{0.h}$ are the base values when the drug input is zero
$Eff_{max,b}$, $Eff_{max,m}$ and $Eff_{max,h}$ are the values of maximum change of concentration to the drug input
C_e^γ is the effect − site concentration
C_{50}^γ is the halfmaximal effective concentration
γ is the Hill′s constant

Proportional-Integral Control (PI Control)

Proportional-Integral control computed the controller output (C_{out}) and gives it to the model. The controller output is mainly influenced by the controller tuning parameters and error (e) [20, 21]. PI control has the integral part to eliminate offset, which is a major disadvantage of Proportional control (P control). The PI control algorithm is computed as shown in equation (10).

$$C_{out} = C_{out_{bias}} + K_c e + \frac{K_c}{\tau_i} \int e \, dt \quad (10)$$

Where C_{out} is the controller output
$C_{out_{bias}}$ is the controller bias
K_c is the controller gain
e is error
τ_i is integral time

The proportional term in the controller gets summed up or eliminated from $C_{out_{bias}}$ based on the controller error size for each time (t). The function of integral term is to make continuous summing of past errors and present errors. To determine the tuning parameters, initially the open loop response of the PK-PD model is taken. From the graph obtained as shown in Figure 2, time constants t_1 and t_2 are calculated at 28.3% and 63.2% of the overall response. The values of t_1 and t_2 are sued to determine the tuning parameters from the equations (11)-(15).
Time constant, $\tau = 0.5(t_2 - t_1)$ (11)

Time delay, $t_d = (t_2 - \tau)$ (12)

Process gain, $K_p = \left(\frac{\Delta output}{\Delta input}\right)$ (13)

Controller gain, $K_c = \left(\frac{0.9\tau}{t_d K_p}\right)$ (14)

Integral time, $\tau_i = (3.33 t_d)$ (15)

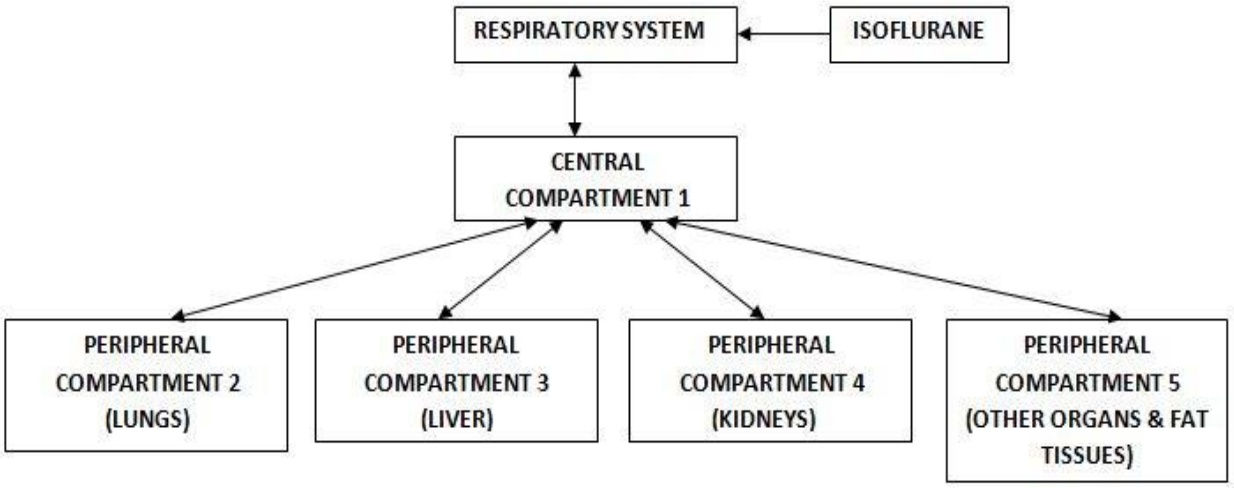

Figure 1: Structure of Pharmacokinetic – Pharmacodynamic (PK-PD) Model

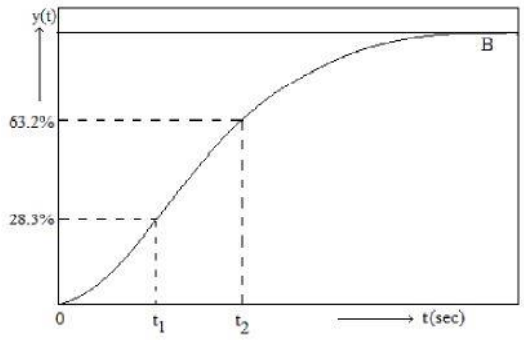

Figure 2: Open loop curve to determine the controller parameters

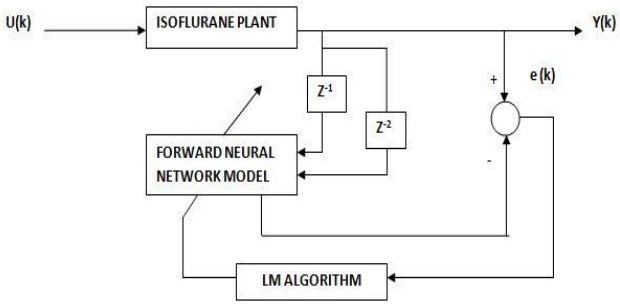

Figure 3: Block representation forward NN model

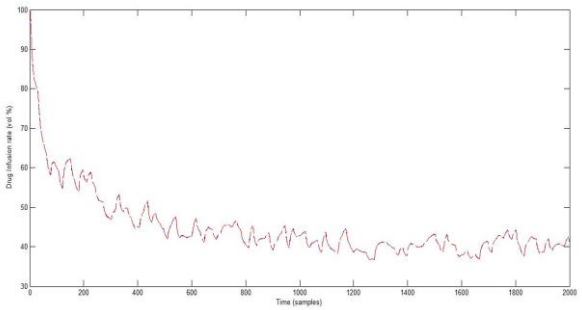

Figure 4: Training and validation of forward NN model for BIS

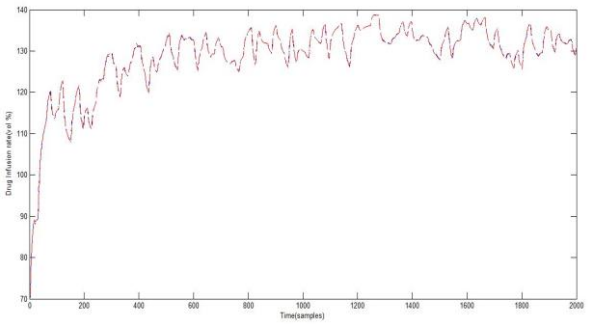

Figure 5: Training and validation of forward NN model for MAP

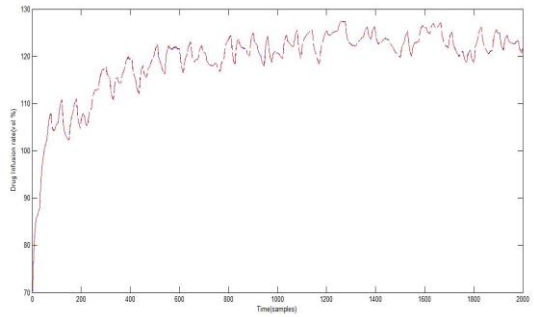

Figure 6: Training and validation of forward NN model for HR

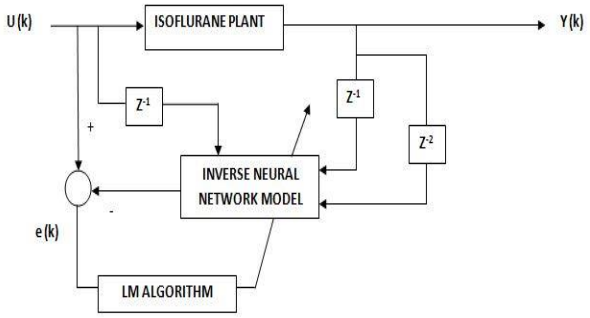

Figure 7: Block representation inverse NN model

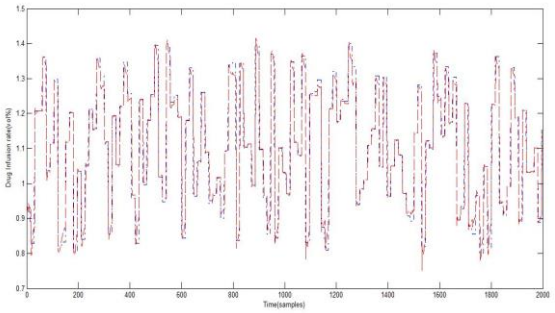

Figure 8: Training and validation of inverse NN model for BIS

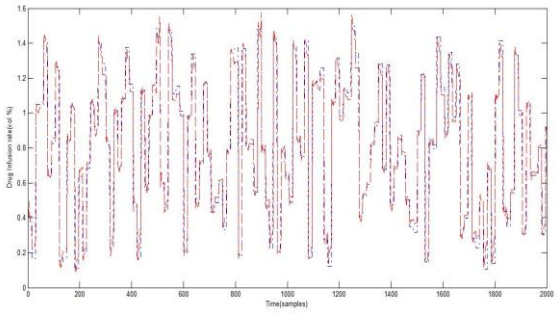

Figure 9: Training and validation of inverse NN model for MAP

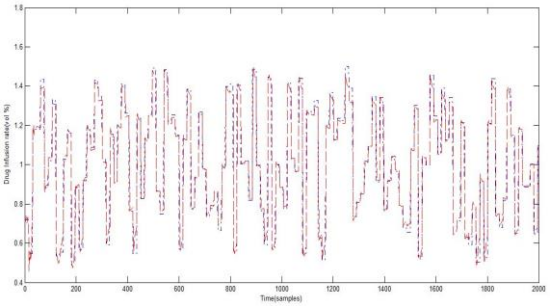

Figure 10: Training and validation of inverse NN model for HR

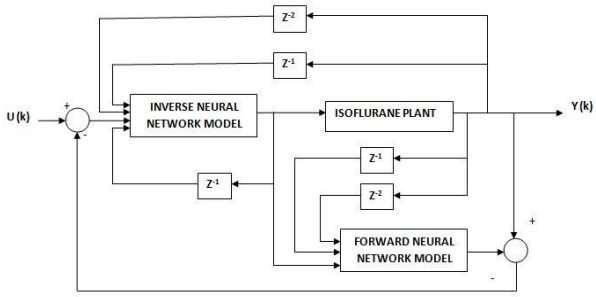

Figure 11: Block representation of neural network based internal model control

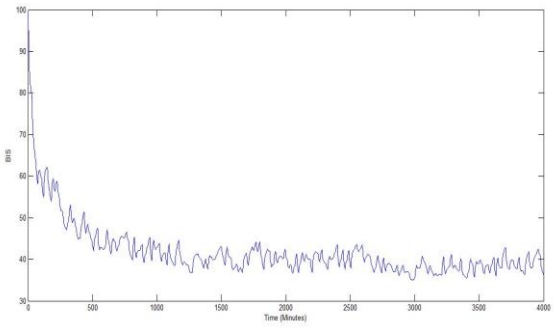

Figure 12: Open loop response of BIS

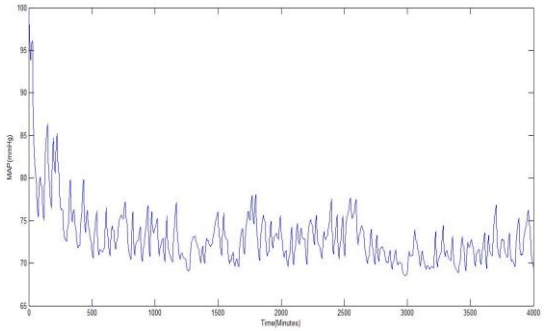

Figure 13: Open loop response of MAP

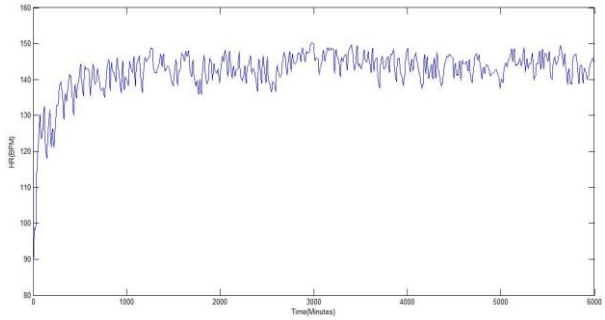

Figure 14: Open loop response of HR

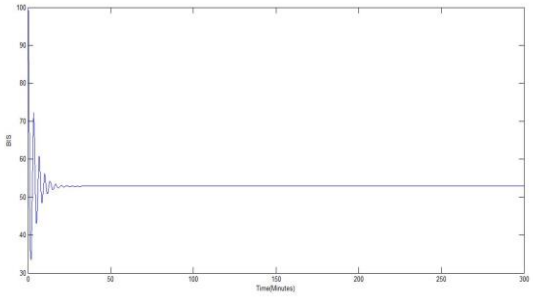

Figure 15: Closed loop response of BIS by PI Control

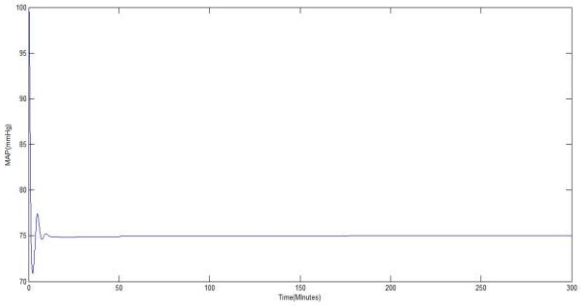

Figure 16: Closed loop response of MAP by PI Control

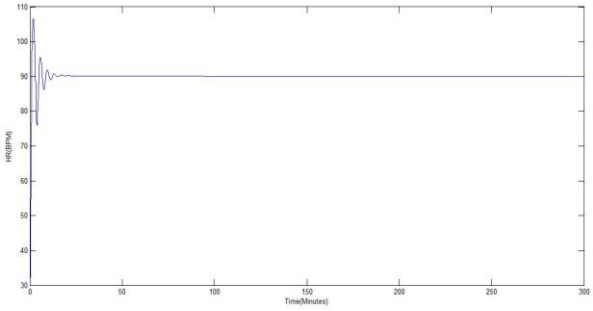

Figure 17: Closed loop response of HR by PI Control

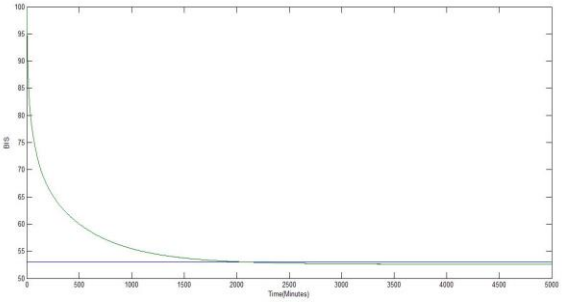

Figure 18: Closed loop response of BIS by NNIM Control

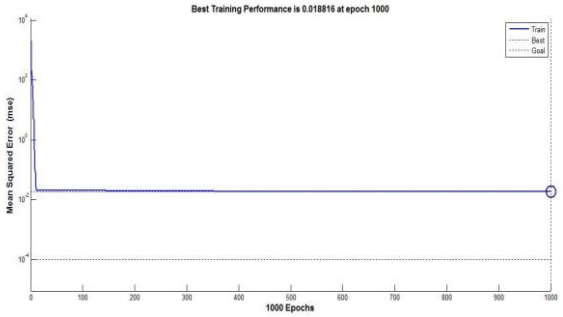

Figure 19: Performance measure of BIS by NNIM Control

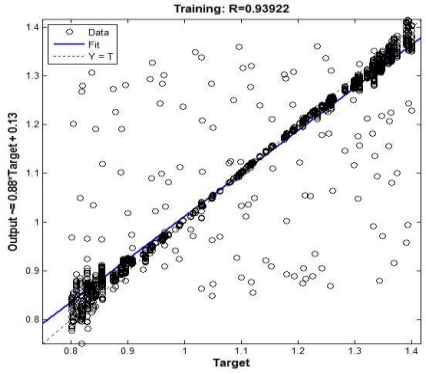

Figure 20: Regression state of BIS by NNIM Control

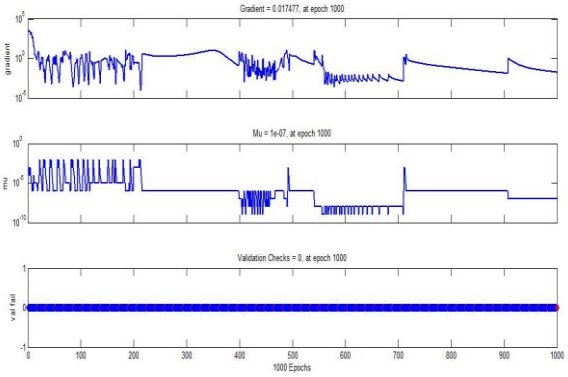

Figure 21: Training state measure of BIS by NNIM Control

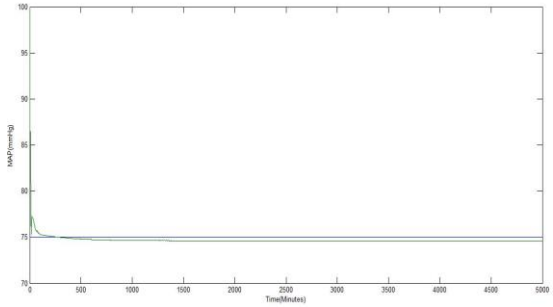

Figure 22: Closed loop response of MAP by NNIM Control

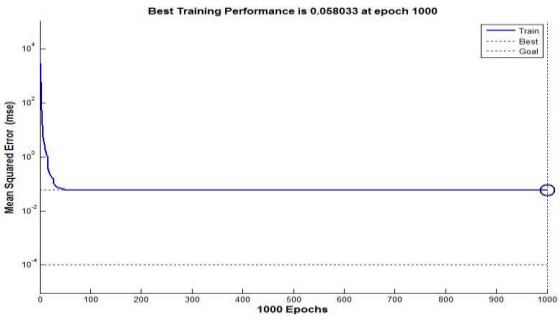

Figure 23: Performance measure of MAP by NNIM Control

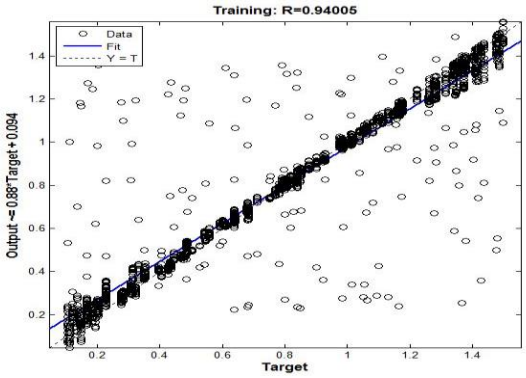

Figure 24: Regression state of MAP by NNIM Control

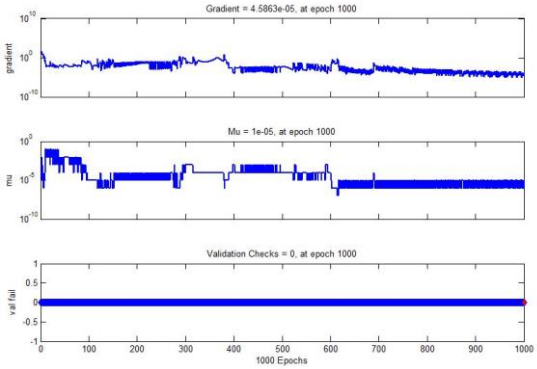

Figure 25: Training state measure of MAP by NNIM Control

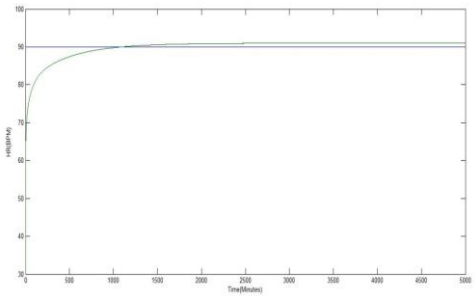

Figure 26: Closed loop response of HR by NNIM Control

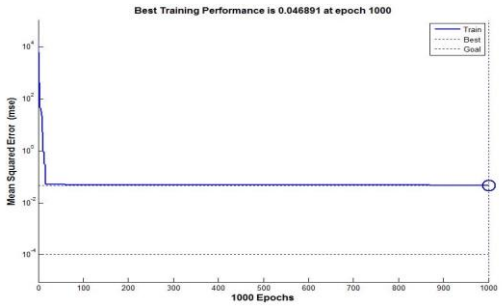

Figure 27: Performance measure of HR by NNIM Control

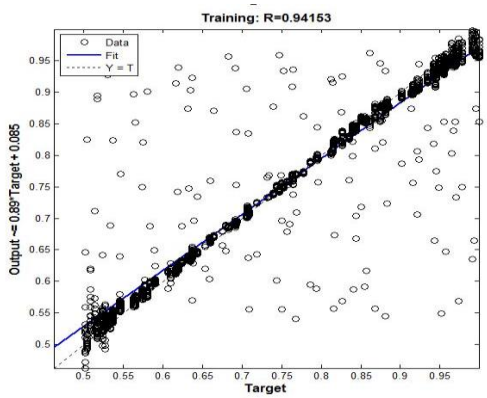

Figure 28: Regression state of HR by NNIM Control

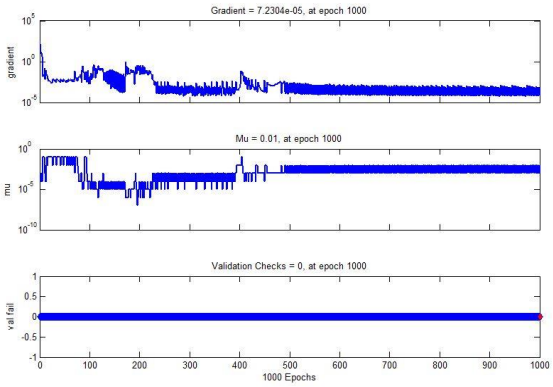

Figure 29: Training state measure of HR by NNIM Control

Neural Network based Internal Model Control (NNIMC Control)

Artificial Neural Network is used in biomedical systems where the output of the network is trained in such a way to get the desired values by adjusting the input weights. The training process of the neural network requires a proper set of input data and target output. The hidden layer in the network is sued to behave as the intermediate between the process input and network trained output. The learning algorithm is used to train the network based on the input given to the system [22]. During training the weights are adjusted iteratively to improve the performance of the network. Mean Square Error is the performance indices used in NNIMC Control. The design of NNIMC involves forward model and inverse model.

Training and Validation of Forward Neural Network Model

This model is used to train the forward dynamics of the PK-PD model. The Levenberg-Marquardt algorithm is used to train the forward NN model. The training of the network is done with delayed outputs and present inputs. The activation function used for hidden layer is transigmoidal and for output layer is linear function. Based on the external input given to the system as shown in Figure 3, the forward NN model is trained and the validation results are shown in Figures 4, 5 and 6.

Training and Validation Inverse Neural Network Model

This method is used to train the inverse dynamics of the PK-PD model. The NN is trained with past input and output to predict the future and present process input. Levenberg-Marquardt algorithm is used to train the inverse NN model [23]. Since the input and output data matches together, this leads to the development of model-based controllers as shown in Figure 7. The validation results are shown in Figures 8, 9 and 10.

Internal Model Control (IMC)

The IMC structure generally consists of three blocks such as controller, internal model and internal model loop. The IMC principle states that the proper control mechanism can be executed for the process only if the control system enfolds the description of the process directly or indirectly. The internal model block is the reference model to that of the process which is to predict the process output [24]. The variation between the plant output and model output is computed by the internal model loop as shown in Figure 11. Another important objective of IMC is that the ultimate control stratagem can be established only if a precise model of the process is used.

RESULTS AND DISCUSSION

In this section, the closed loop responses of PI control are shown in Figures 15, 16 and 17. The drug inspiration for physiological variables administration is taken in the range of 0.5 to 1.5 % of isoflurane. The nominal range of BIS is 40-60, for MAP is 60-100 mmHg and for heart rate is 60-100 BPM. Open loop response of the PK-PD model is shown in Figures 12, 13 and 14.

The simulation results of NNIMC are shown in the following figures and their respective performance measure, regression ad their training state are also compared below.

CONCLUSION

Automatic management of drug infusion provides safer platform for the patient's speedy recovery, reduction in the amount of drugs utilized and their complications. This also reduces the cost and time of the patient to be spent in post surgical treatments. From the simulation results, it is deduced that NNIMC has intensified the performance over PI control in simultaneous regulation of BIS, MAP and HR. The model can be further enhanced with optimization techniques.

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