MODEL BASED DRUG DELIVERY FOR ANESTHESIA

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Abstract: In this work a compartmental model for delivery of three drugs (isoflurane, dopamine and sodium nitroprusside) for anesthesia is presented. The key feature of this model is that mean arterial pressure and unconsciousness of the patient can be simultaneously regulated. A number of dynamic simulation experiments are carried out for the validation of the model.

Keywords: Biomedical systems, modelling, compartmental model, anesthesia, multiple drug infusion, mean arterial pressure (MAP), bispectral index (BIS)

1. INTRODUCTION

Anesthesia is defined as the absence or loss of sensation. To provide safe and adequate anesthesia, the anesthesiologist must ensure muscle relaxation and hypnosis, guarantee analgesia and maintain vital functions of the patient. Muscle relaxation is necessary to assist access to internal organs and to depress movement response to surgical stimulation. The unconsciousness and the absence of postoperative recall of events that occur during surgery are referred to as hypnosis or depth of anesthesia. The level of hypnosis can be estimated by Bispectral Index (BIS), which is based upon the principle of electroencephalogram and is the only non-invasive measure of central nervous system activity while the patient is unconscious. Analgesia is characterized by pain relief and there are no specific techniques for its quantification. During the surgery a wide range of vital functions, such as mean arterial pressure (MAP), heart rate and cardiac output (CO), should be monitored and maintained within the desired ranges. Note that not all the vital functions can be measured directly and hence are inferred indirectly. These vital functions are maintained by the anesthesiologist by regularly infusing various anesthetic drugs and/or intravenous fluids. It must be emphasized that a tight control of these vital functions has paramount consideration; otherwise it may lead to fatal situations (Simpson and Popat, 2002).

Automation of anesthesia for monitoring of vital functions is desirable as it will provide more time and flexibility to the anesthesiologist to focus on critical issues, monitor the conditions that cannot be easily measured and overall improve patient's safety. Also, the cost of the drugs will be reduced and shorter time will be spent in the post-operative care unit. A number of models and control strategies have been reported in the open literature for anesthesia (e.g. Derighetti *et al.,* 1997; Zwart *et al.,* 1972; Yasuda *et al.,* 1989-1991; Gopinath *et al.,* 1995; Rao *et al.*, 2001; Mahfouf *et al.*, 2003). Gentilini *et al.* (2001) proposed a model for the regulation of MAP and hypnosis with isoflurane. It was observed that controlling both MAP and hypnosis simultaneously with isoflurane was difficult. Yu *et al.* (1990) proposed a model for regulating MAP and CO using

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dopamine (DP) and sodium nitroprusside (SNP), but the control of hypnosis was not considered.

In this work, a compartmental model is proposed, which allows the simultaneous regulation of the MAP and the unconsciousness of the patients. Three major aspects characterise the model: (i) pharmacokinetics, which describes the uptake and distribution of the drugs, (ii) pharmacodynamics which is concerned with the effect of the drugs on the vital functions and (iii) baroreflex which accounts for the reaction of the central nervous system to changes in the blood pressure. The model involves choice of three drugs, isoflurane, DP and SNP. This combination of drugs allows simultaneous regulation of MAP and hypnosis.

2. MODELLING ANESTHESIA

The model is based on the distribution of isoflurane in the human body (Yasuda *et al.*, 1991) and the works of Gentilini *et al.* (2001) and Yu *et al*. (1990). It consists of five compartments organized as shown in Figure 1.

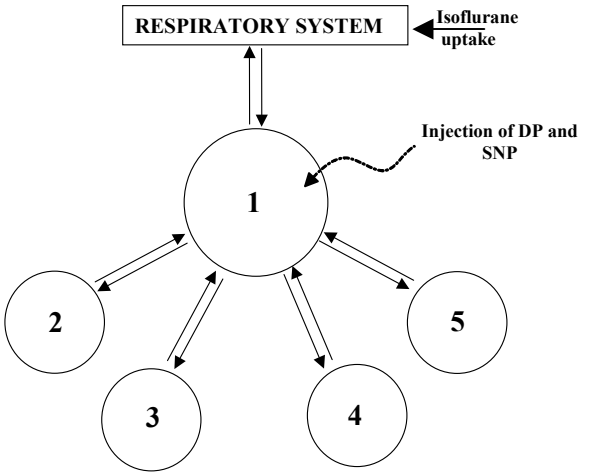

Fig. 1. Compartmental Model

The compartments stand for:

1: Lungs
2: Vessel Rich organs (e.g. liver)
3: Muscles
4: Other organs and tissues
5: Fat tissues

Isoflurane is a volatile drug that first enters the respiratory system and then the lungs. SNP and DP are intravenous drugs; SNP is a vasodilator that dilates the arteries and effectively lowers MAP and DP is an inotropic agent that enhances the cardiac performance by improving the heart contractility. These drugs are distributed to the compartments via the circulatory system and therefore the heart can also be taken as if belonging to the central compartment. The transfers from the central compartment to the peripheral compartments *i.e.* compartments 2-5 occur via the arteries and the transfers from the peripheral compartments to the central, via the veins. The introduction of drugs can be related to the first compartment as shown in Figure 1.

2.1 Pharmacokinetic Modelling

Respiratory System. The uptake of isoflurane in central compartment occurs via the respiratory system. Considering a well-stirred system, this is modelled as:

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

where C_{insp} is the concentration of isoflurane inspired by the patient (g/mL), C_{in} is the concentration of isoflurane in the inlet stream (g/mL), 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).

Central Compartment. The distribution of isoflurane within the central compartment is governed by:

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

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).

The infusion of intravenous drugs DP and SNP in the central compartment is modelled as follows:

$$V_1\frac{dC_1}{dt} = \sum_{i=2}^{5}\left(Q_i\left(\frac{C_i}{R_i} - C_1\right)\right) + C_{\inf} - \frac{1}{\tau_{1/2}}C_1V_1$$

where C_{inf} is the flowrate of the drug infused (g/min), V_i is the volume of compartment i (mL) and $\tau_{1/2}$ is the half life of the drug (min).

Peripheral Compartments. Elimination of isoflurane by exhalation and metabolism in liver, the 2nd compartment, is given by:

$$V_2\frac{dC_2}{dt} = Q_2\left(C_1 - \frac{C_2}{R_2}\right) - k_{20}C_2V_2$$

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

The concentration of isoflurane in compartments 3 to 5 is given by

$$V_i \frac{dC_i}{dt} = Q_i\left(C_1 - \frac{C_i}{R_i}\right), \; i = 3,\ldots,5.$$

DP and SNP naturally decay in the body, hence the equations for compartments 2 to 5 are

$$V_i \frac{dC_i}{dt} = Q_i\left(C_1 - \frac{C_i}{R_i}\right) - \frac{1}{\tau_{1/2}} C_i V_i \; , \; i = 2,\ldots,5.$$

2.2 Pharmacodynamic Modelling

Effect of DP and SNP on MAP. DP and SNP indirectly affect MAP via two of the heart's characteristic parameters: maximum elastance (E_{max}) and systemic resistance (R_{sys}). The action of these two drugs on these parameters is given by:

$$\frac{dEff}{dt} = k_1 C_1^N \left(Eff_{\max} - Eff\right) - k_2 Eff$$
$$E_{\max} = E_{\max,0}\left(1 + Eff_{DP-E_{\max}}\right)$$
$$R_{sys} = R_{sys,0}\left(1 - Eff_{DP-R_{sys}} - Eff_{SNP-R_{sys}}\right)$$

where *Eff* is the measure of the effect of drug on the parameters of interest, R_{sys} is the systemic resistance (mmHg/(mL/min)), E_{max} is the maximum elastance (mmHg/mL), $E_{max,0}$ is nominal maximum elastance, $R_{sys,0}$ is nominal systemic resistance, $Eff_{DP\text{-}Emax}$ is effect of DP on E_{max}, $Eff_{DP\text{-}Rsys}$ is effect of DP on R_{sys}, $Eff_{SNP\text{-}Rsys}$ is the effect of SNP on R_{sys}, k_1, k_2 are the rate constants and N is the non-linearity constant.

MAP can be expressed as a function of E_{max} and R_{sys} as:

$$MAP^2 \frac{1}{R_{sys}^2} + 2K^2 MAP - 2K^2 V_{LV} E_{\max} = 0$$
$$K = \frac{A_{aorta} A_{LV}}{\sqrt{\rho}\sqrt{A_{LV}^2 - A_{aorta}^2}}$$

where *MAP* is the mean arterial pressure (mmHg), A_{aorta} is the cross sectional area of the aorta (cm^2), A_{LV} is the cross sectional area of the left ventricle (cm^2), V_{LV} is the mean volume of the left ventricle (mL) and ρ is the blood density (g/mL).

Effect of Isoflurane on MAP. Isoflurane affects MAP as follows:

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

where, $g_{i,0}$ are the baseline conductivities (mL/(min.mmHg)) and b_i are the variation coefficients of conductivity (mL/g).

Effect of Isoflurane on BIS. There is experimental evidence that a transportation delay exists between the lungs and the site of effect of isoflurane. To model this, an effect compartment is linked to the central compartment. The concentration of isoflurane within this compartment is related to the central compartment, which is given by:

$$\frac{dC_e}{dt} = k_{e0}\left(C_1 - C_e\right)$$

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 can be then expressed as follows:

$$\Delta BIS = \Delta BIS_{MAX} \frac{C_e^\gamma}{C_e^\gamma + EC_{50}^\gamma}$$
$$\Delta BIS = BIS - BIS_0$$
$$\Delta BIS_{MAX} = BIS_{MAX} - BIS_0$$

where BIS_0 is the baseline value of BIS (assumed to be 100), BIS_{MAX} represents the minimum value of BIS (assumed to be 0), EC_{50} is the patient's sensitivity to the drug and γ is the measure of the degree of non-linearity.

2.3 Baroreflex

In this model, baroreflex is obtained from a set of transfer functions relating the mean arterial pressure to the maximum elastance and the systemic resistance and is given by:

$$bfc = \frac{e^{c(MAP - MAP0)}}{1 + e^{c(MAP - MAP0)}}$$

where *c* is the empirical constant (mmHg).

The nominal values of the parameters used in this model are given in Table 1 in the appendix. These parameter values are based upon the values reported in the literature for the various organs, within a compartment.

3. MODEL VALIDATION

A number of dynamic simulations were performed using gPROMS (2003) to validate the model. First, a simulation was carried out to see the effect of isoflurane on MAP and BIS. Figure 2 shows the profile of MAP when subjected to an uptake of 1% vol. of isoflurane.

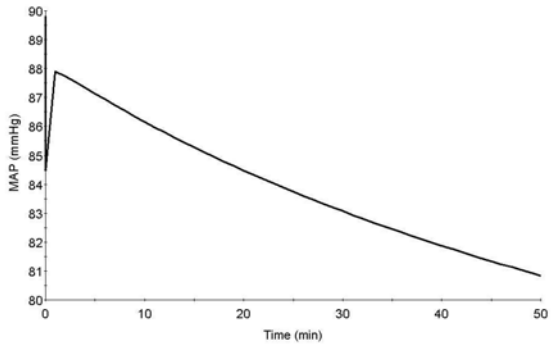

Fig. 2. MAP response to an uptake of 1% vol. of isoflurane

Figure 3 shows the drop in BIS when there is an uptake of 1% vol. of isoflurane and then an increase in BIS at 1000 minutes when there is no uptake of isoflurane. It is observed that BIS drops to 40 for an isoflurane uptake of 1% vol.

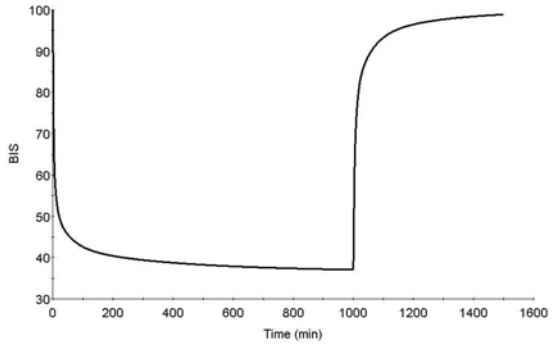

Fig. 3. BIS response to an uptake of 1% vol. of isoflurane

Another simulation was performed to see the effect on BIS when subjected to an uptake of 0.5% vol. of isoflurane. Figure 4 shows the performance where it is observed that BIS reaches a value of 65. General anesthesia corresponds to BIS value between 40 and 65. Hence, this range can be maintained by an uptake of isoflurane between 0.5% and 1% vol.

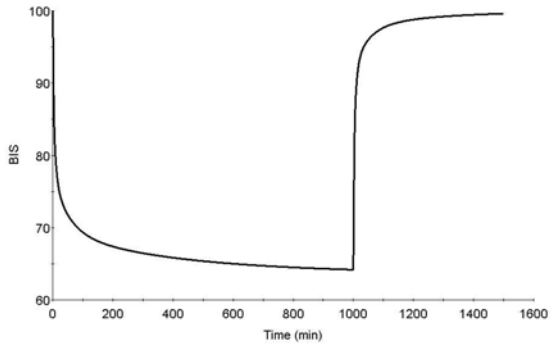

Fig. 4. BIS response to an uptake of 0.5% vol. of isoflurane

To see the effect of dopamine on MAP, a simulation was performed, where the model was run at steady state for the first 10 minutes, then a drop of 20 mmHg in MAP was induced and finally 10 minutes after the drop, 5 μg/kg/min of dopamine was infused. Figure 5 shows that MAP decreases to 70 mmHg after the drop and then increases to approximately 82 mmHg due to the baroreflex and then finally reaches the steady state after the infusion of dopamine.

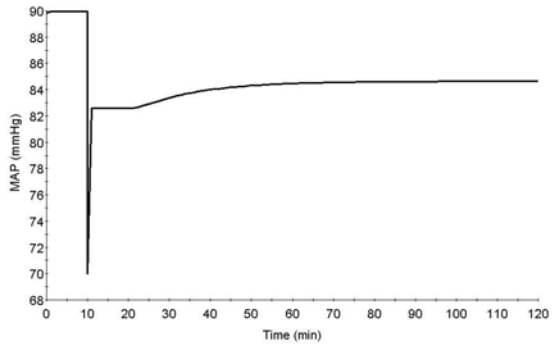

Fig. 5. DP infusion in response to a drop in MAP

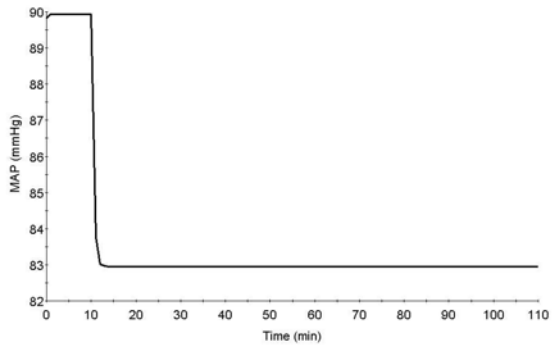

Fig. 6. MAP response to a continuous injection of 1 μg/kg/min of SNP after 10 minutes

Similarly, simulations were performed to see the effect of SNP on MAP. It was observed that 1 μg/kg/min of SNP results in a drop in MAP from 90 mmHg to 83 mmHg (Figure 6) and 10 μg/kg/min decreases MAP to approximately 69 mmHg (Figure 7).

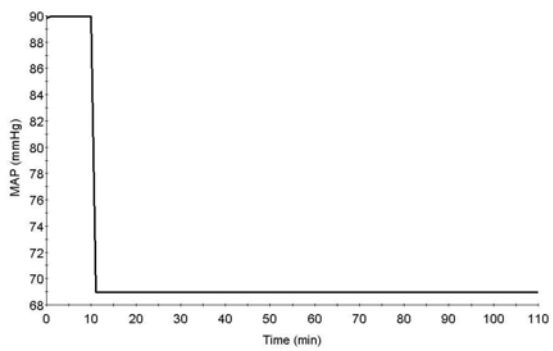

Fig. 7. MAP response to a continuous injection of 10 μg/kg/min of SNP after 10 minutes

To validate the model's general behaviour, an anaesthetic procedure has been simulated, which consists of five parts. For the first 10 minutes, it is assumed that the patient is awake. Then 0.8% vol. of isoflurane is infused alongwith 0.7 μg/kg/min of SNP to attain the anesthetic state and lower the blood pressure to 60 mmHg. After 800 minutes, when the steady state is reached, a drop of 20 mmHg in MAP is induced. It was assumed for the sake of simulation that the anaesthesiologist would react only after 5 minutes of the drop by giving an infusion of 4.5 μg/kg/min of DP to counteract the drop. Then after 60 minutes, MAP does not drop and hence DP infusion was stopped. After another 40 minutes, the uptake of isoflurane and SNP was stopped and it was observed that the patient smoothly wakes up. Figures 8 and 9 shows the results of this simulation.

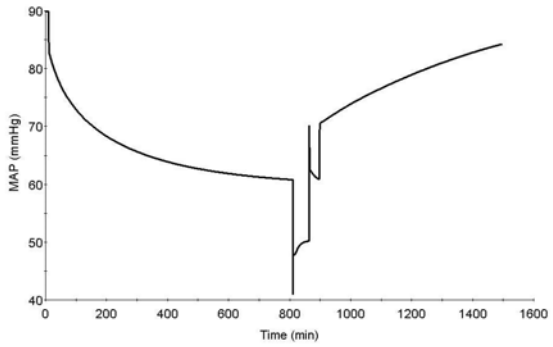

Fig. 8. Simulation of the regulation of MAP during anesthesia

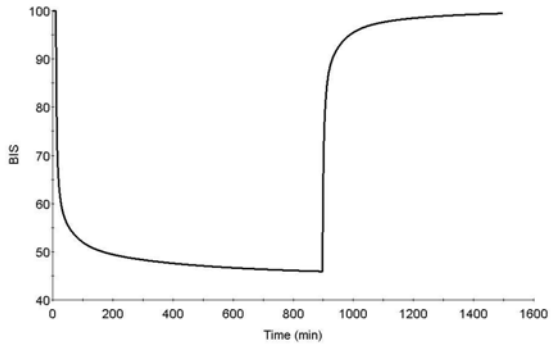

Fig. 9. Simulation of the regulation of BIS during anesthesia

It must be stressed that this procedure is oversimplified. First, the anesthesiologist would give high dosages of drugs at the beginning of the procedure to induce quick response from the patient and then gradually adjust the infusions to keep BIS, MAP and infusion rates within safe ranges. Also, the patient would be subject to greater number of disturbances starting with the intubation at the beginning of procedure, which was not considered in this simulation. Despite these simplifications, it was observed that the accuracy of the model is not altered by multiple drug infusions.

It is well known that the surgical operations are subject to a number of disturbances and uncertainties such as blood losses and variations in model parameters from nominal values. In this work, a number of dynamic simulation studies have been reported at the nominal patient model parameter values to validate the applicability of the model to simultaneously regulate MAP and hypnosis. A successful development of automatic controller for anesthesia will therefore rely on developing control strategies that can take into account the uncertainty in patient model parameters and can also reject the disturbances, and is the focus of the current work.

4. CONCLUDING REMARKS

Automation of anesthesia is expected to allow the anesthesiologist to focus more on critical aspects during surgery and reduce the amount of drugs infused and the time spent by the patient in the post-operative care unit. A successful implementation of the automation strategy relies on a hi-fidelity model, which can capture the dynamic response of the patient to various drug infusions. In this work, a compartmental model for anesthesia that takes into account simultaneous regulation of MAP and unconsciousness of the patients has been developed and validated. This paves the way for the development of advanced control and automation strategies for anesthesia.

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APPENDIX

Table 1 Model Parameters

Model Parameters	Value	Units
A_{aorta}	4.15	cm^2
A_{lv}	12	cm^2
b_1	0	mL/g
b_2	435.2574	mL/g
b_3	4194.299	mL/g
b_4	3205.077	mL/g
b_5	-1345.34	mL/g
BIS_0	100	
BIS_{MAX}	0	
c	0.06263	mmHg
EC_{50}	6.15E-5	
Eff_{max} (DP on E_{max})	1.3	
Eff_{max} (DP on R_{sys})	0.5	
Eff_{max} (SNP on R_{sys})	0.635	
$E_{max,0}$	2.12	mmHg/mL
f_R	14.5	min^{-1}
$g_{1,0}$	0	mL/(min.mmHg)
$g_{2,0}$	24.456	mL/(min.mmHg)
$g_{3,0}$	8.412	mL/(min.mmHg)
$g_{4,0}$	4.667	mL/(min.mmHg)
$g_{5,0}$	1.247	mL/(min.mmHg)
k_{20}	0.0093	min^{-1}
k_{e0}	0.948	min^{-1}
K	4.316	$cm^{7/2}.g^{1/2}$
$MAP0$	90	mmHg
R_1	1.59	
R_2	1.4	
R_3	2.92	
R_4	44.9	
R_5	44.9	
$R_{sys,0}$	0.0258	mmHg/(mL/min)
V	5000	mL
V_1	2310	mL
V_2	7100	mL
V_3	11300	mL
V_4	3000	mL
V_5	5100	mL
V_{lv}	85	mL
V_T	500	mL
Δ	150	mL
ΔQ	300	mL/min
γ	1.6	
ρ	1.05	g/mL
$\tau_{1/2}$ (DP)	2	min
$\tau_{1/2}$ (SNP)	0.25	min