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ORIGINAL ARTICLE

Modelling and multi-parametric control for delivery of anaesthetic agents

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Abstract This article presents model predictive controllers (MPCs) and multi-parametric model-based controllers for delivery of anaesthetic agents. The MPC can take into account constraints on drug delivery rates and state of the patient but requires solving an optimization problem at regular time intervals. The multi-parametric controller has all the advantages of the MPC and does not require repetitive solution of optimization problem for its implementation. This is achieved by obtaining the optimal drug delivery rates as a set of explicit functions of the state of the patient. The derivation of the controllers relies on using detailed models of the system. A compartmental model for the delivery of three drugs for anaesthesia is developed. The key feature of this model is that mean arterial pressure, cardiac output and unconsciousness of the patient can be simultaneously regulated. This is achieved by using three drugs: dopamine (DP), sodium nitroprusside (SNP) and isoflurane. A number of dynamic simulation experiments are carried out for the validation of the model. The model is then used for the design of model predictive and multi-parametric controllers, and the performance of the controllers is analyzed.

Keywords Compartmental model · Model predictive control · Multi-parametric control · Delivery of anaesthetic agents

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1 Introduction

Adequate general anaesthesia can be defined as a reversible pharmacological state where it is guaranteed that the triad of anaesthesia, given by muscle relaxation, analgesia and hypnosis, is achieved and the vital functions such as mean arterial pressure (MAP), heart rate and cardiac output (CO), are monitored and maintained within the desired ranges.

Note that not all the vital functions can be measured directly, and hence are inferred indirectly and are maintained by the anaesthesiologist by regularly infusing various anaesthetic 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 [27]. Automation of anaesthesia for monitoring of vital functions is desirable as it will provide more time and flexibility to the anaesthesiologist 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. An efficient implementation of automation strategies for biomedical systems relies on

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developing models [9] and model predictive controllers (MPCs) for such systems.

For anaesthesia, some of the models that have been reported in the open literature are: (i) pharmacokinetic and pharmacodynamic model of Zwart et al. [34] for uptake of halothane, a volatile anaesthetic, and its influence on CO and MAP, (ii) five-compartment model of Yasuda et al. [29–31] for the distribution of isoflurane, a volatile anaesthetic, and (iii) circulatory model of Yu et al. [32] for haemodyanmic repsonses to intravenous agents, dopamine (DP) and sodium nitroprusside (SNP), in case of an acute heart failure.

The controllers for anaesthesia can be broadly classified based upon their application for: (i) regulation of hemodynamic variables [2, 8, 12, 13, 16, 18, 26, 28, 32–34] and (ii) simultaneous regulation of haemodynamic and other states of anaesthesia [1, 11, 17, 20]. Control of anaesthesia is based upon reliable measurements and estimation of state variables. Recently Huang et al. [15] proposed using a heart rate variability parameter for estimating anaesthetic depth for isoflurane infusion.

The recent study in the area of modelling and control of anaesthesia can be summarized as follows. Caruso et al. [4] modelled the effect of remifentanil on breathing and showed that their controller maintains CO_2 set point in the presence of disturbances. Gentilini et al. [11] proposed a model for the regulation of mean arterial pressure (MAP) and hypnosis with isoflurane—it was observed that controlling both MAP and hypnosis simultaneously with isoflurane was difficult. Yu et al. [32] proposed a model for regulating MAP and cardiac output (CO) using dopamine (DP) and sodium nitroprusside (SNP), but the control of hypnosis was not considered. In this article, a compartmental model is proposed, which allows the simultaneous regulation of MAP, CO and the unconsciousness of the patients. This model acts as a basis for the derivation of model predictive and multi-parametric controllers. Three major aspects characterize the model:

(1) pharmacokinetics which describes the uptake and distribution of the drugs
(2) pharmacodynamics which is concerned with the effect of the drugs on the vital functions
(3) 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 the drugs allows simultaneous regulation of MAP, CO and hypnosis. The rest of the article is organized as follows. The proposed modelling and control methodology is presented in the next section, and the results for model validation and control are presented in Sect. 3. A discussion of results is given in Sect. 4.

2 Methods

2.1 Modelling anaesthesia

The model is based on the distribution of isoflurane in the human body [30, 31] and on the studies of [11, 32]. It consists of five compartments organized as shown in Fig. 1. The compartments stand for: Lungs, Vessel Rich organs (e.g. liver), Muscles, Other organs and tissues and Fat tissues respectively. Isoflurane is a volatile drug that first enters the respiratory system and then the lungs whereas SNP and DP are intravenous drugs. These drugs are distributed to the compartments via the circulatory system and, therefore, the heart can be considered as if it belongs 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 on Fig. 1.

2.1.1 Pharmacokinetic modelling

Assuming that all the compartments are well-stirred, the differential equations resulting from mass balances for a generic ith compartment can be written as

$$V_i \frac{dC_{i,j}}{dt} = Q_i \left(C_{a,j} - \frac{C_{i,j}}{R_i} \right) - k_{i,j} C_{i,j}$$

where V_i is the volume of compartment i, $C_{i,j}$ is the concentration of the drug j in the compartment i, Q_i is the blood flow to the compartment i, $k_{i,j}$ is the relevant rate constant, $C_{a,j}$ is the drug concentration in the arterial pool and R_i is the partition coefficient between blood and tissues

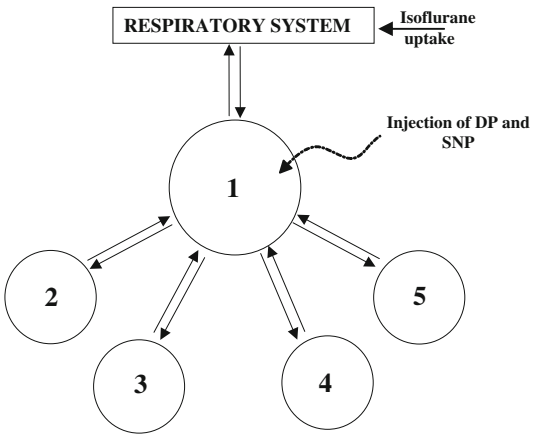

Fig. 1 Compartmental model: compartment 1 is the central compartment and refers to the heart and compartments 2–5 are the peripheral compartments referring to vessel rich organs, muscles, other organs and tissues and fat tissues

in compartment i. The partition coefficient R_i defines the ratio of blood, which will be kept by the living tissue constituting the ith compartment. Its role is not to modulate the concentration of drug, but the flow rate of blood according to the following relation:

$$Q_{i,\text{out}} = \frac{Q_{i,\text{in}}}{R_i}$$

where $Q_{i,\text{in}}$ is the inlet flow rate of blood (i.e. Q_i), and $Q_{i,\text{out}}$ is the outlet flow rate of blood. Considering the organization of the compartment, the concentration of the drug in the arteries is equal to the concentration in the outlet flows from compartment 1, i.e. the concentration of drug within this well-stirred compartment. Thus, the above equation becomes

$$V_i \frac{\mathrm{d}C_{i,j}}{\mathrm{d}t} = Q_i \left(C_{1,j} - \frac{C_{i,j}}{R_i} \right) - k_{i,j} C_{i,j}$$

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

$$V \frac{\mathrm{d}C_{\text{insp}}}{\mathrm{d}t} = Q_{\text{in}} C_{\text{in}} - (Q_{\text{in}} - \Delta Q) C_{\text{insp}} - f_{\text{R}} (V_{\text{T}} - \Delta) (C_{\text{insp}} - C_{\text{out}})$$

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 (1/min), V_{T} is the tidal volume (ml) and Δ is the physiological dead space (ml).

2.1.1.2 Central compartment The distribution of isoflurane within the central compartment is governed by

$$V_1 \frac{\mathrm{d}C_1}{\mathrm{d}t} = \sum_{i=2}^{5} \left(Q_i \left(\frac{C_i}{R_i} - C_1 \right) \right) + f_{\text{R}} (V_{\text{T}} - \Delta)(C_{\text{insp}} - C_1)$$

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 and 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:

$$V_1 \frac{\mathrm{d}C_1}{\mathrm{d}t} = \sum_{i=2}^{5} \left(Q_i \left(\frac{C_i}{R_i} - C_1 \right) \right) + C_{\text{inf}} - \frac{1}{\tau_{1/2}} C_1 V_1$$

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).

2.1.1.3 Peripheral compartments Elimination of isoflurane by exhalation and metabolism in liver, the 2nd compartment, is given by

$$V_2 \frac{\mathrm{d}C_2}{\mathrm{d}t} = Q_2 \left(C_1 - \frac{C_2}{R_2} \right) - k_{20} C_2 V_2$$

where k_{20} is the rate of elimination of isoflurane in the 2nd compartment (min^{-1}). The concentration of isoflurane in compartments 3–5 is given by

$$V_i \frac{\mathrm{d}C_i}{\mathrm{d}t} = Q_i \left(C_1 - \frac{C_i}{R_i} \right),\ i = 3, \ldots, 5.$$

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

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

2.1.1.4 Blood flows The average change in regional blood flows under the uptake of isoflurane can be computed from the literature [5]. These flows depend on the concentration of this anaesthetic agent.

$$Q_i = Q_{i0} \cdot (1 + \Delta_{\text{flowi}} \cdot C_{\text{in}}), \quad i = \{2, 3, 4, 5\}$$

$$Q_1 = \sum_{i=2}^{5} Q_i$$

where Δ_{flowi} is the ratio of flow rate change in the ith compartment and C_{in} is the concentration of isoflurane in the inlet flow of the respiratory system.

2.1.2 Pharmacodynamic modelling

2.1.2.1 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}, the heart's contractility, maximum pressure/volume ratio in the left ventricle) and Systemic Resistance (R_{sys}, resistance of tissues to blood flow)—and Cardiac Output (CO) (blood volume injected by the heart on a minute basis, l/min). The equation dictating the relationship between blood pressure and cardiac output is

$$\text{MAP} = R_{\text{sys}} \cdot \text{CO}.$$

These physiological variables MAP and CO, the so-called haemodynamic variables, are considered to be highly interconnected in many ways. SNP is a vasodilator drug, administered to control hypotension during anaesthesia in surgery. It causes relaxation of arterial and venous smooth muscles, leading to a rapid and predictable decrease in blood pressure and providing a nearly bloodless surgical field. More specifically, it is known to act principally on R_{sys}, causing an important reduction in it, while it causes a mild reduction on CO, thus leading to an overall decrease in

MAP. DP is an inotropic agent, infused to cure "septic shock", i.e. hypotension, systemic vasodilation and low cardiac output. Consequently, DP increases CO and R_{sys}, indirectly leading to an overall increase in blood pressure.

The action of these two drugs on these parameters is given by

$$\frac{dEff}{dt} = k_1 C^N (Eff_{max} - Eff) - k_2 Eff$$

where Eff is the measure of the effect of drug on the parameters of interest, k_1, k_2 are the rate constants, N is the non-linearity constant and C refers to the concentration of either DP or SNP.

The affected parameters are related to different aspects of the distribution of drugs in the circulatory system: E_{max} is linked to the concentration of DP in the large arteries, whereas R_{sys} is linked to the concentration of DP and SNP in the small ones. However, considering the compartmental model and the fact that the compartments are considered well-stirred, those two concentrations are equal to the concentration of DP in the central compartment:

$$\frac{dEff}{dt} = k_1 C_1^N (Eff_{max} - Eff) - k_2 Eff.$$

E_{max} and R_{sys} are related to the previous equation as follows:

$$E_{max} = E_{max,0}(1 + Eff_{DP-E_{max}})$$
$$R_{sys} = R_{sys,0}\left(1 - Eff_{DP-R_{sys}} - Eff_{SNP-R_{sys}}\right)$$

where R_{sys} is the systemic resistance (mmHg/(ml/min)), E_{max} is the maximum elastance (mmHg/ml), $E_{max,0}$ is the nominal maximum elastance, $R_{sys,0}$ is the nominal systemic resistance, $Eff_{DP-E_{max}}$ is the effect of DP on E_{max}, $Eff_{DP-R_{sys}}$ is the effect of DP on R_{sys} and $Eff_{SNP-R_{sys}}$ is the effect of SNP on R_{sys}.

2.1.2.2 Relationship between E_{max}, R_{sys} and MAP Applying Bernoulli's equation to the heart, a relation between CO and MAP can be obtained. As E_{max} is the maximum pressure to volume ratio in the left ventricle, it can be related to CO by Bernoulli's equation for two points on the same streamline:

$$P + \frac{1}{2}\rho u^2 = \text{constant}$$

where P is the pressure, ρ is the density and u is the velocity.

It is assumed that gravity effects are negligible, blood density is constant and the flow is steady. The equation should provide a good approximation of the relationship between E_{max} and CO. Also, E_{max} applies to the systolic elastance of the heart, which is the pressure–volume ratio at the height of contraction. This will determine the pressure at which blood is expelled from the left ventricle and can, therefore, be used in this analysis. If the first point on a streamline is in the left ventricle and the second point in the aorta, just after the heart, then for this system

$$V_{LV}E_{max} + \frac{1}{2}\rho\left(\frac{CO}{A_{LV}}\right)^2 = MAP + \frac{1}{2}\rho\left(\frac{CO}{A_{aorta}}\right)^2$$

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) (averaged on a complete cardiac cycle) and ρ is the blood density (g/ml). Rearranging the above equation,

$$CO = K(2V_{LV}E_{max} - 2MAP)^{1/2}$$

where $K = \frac{A_{aorta}A_{LV}}{\sqrt{\rho}\sqrt{A_{LV}^2 - A_{aorta}^2}}$.

Since, $MAP = R_{sys} \cdot CO$, MAP can be expressed as a function of E_{max} and R_{sys} as:

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

2.1.2.3 Effect of isoflurane on MAP The equation describing the haemodynamic effect of isoflurane has been obtained from the modelling structure derived by [29] for halothane, where Ohm's law is applied to the circulatory system, as shown in Fig. 2. Each compartment presents a certain conductance to blood flow, which can be related to MAP and CO as follows:

$$MAP = \frac{CO}{\sum_{i=1}^{n} g_i}$$

where where g_i is the conductance of the ith compartment and n is the total number of compartments. Since,

$$CO = \sum_{i=1}^{n} Q_i \quad \text{and}$$

$$g_i = g_{i,0} \cdot (1 + b_i \cdot C_i)$$

where $g_{i,0}$ is the base conductivity of the ith compartment and b_i is the coefficient of action of isoflurane on the conductivity of the ith compartment, isoflurane affects MAP as follows:

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

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

2.1.2.4 Effect of isoflurane on BIS There is experimental evidence supporting that a transportation delay exists between the lungs and the site of effect of isoflurane. In order to model this, an effect compartment is linked to the central compartment. Assuming that this new compartment has negligible volume, the mass balances derived so far remain the same. The concentration of isoflurane within

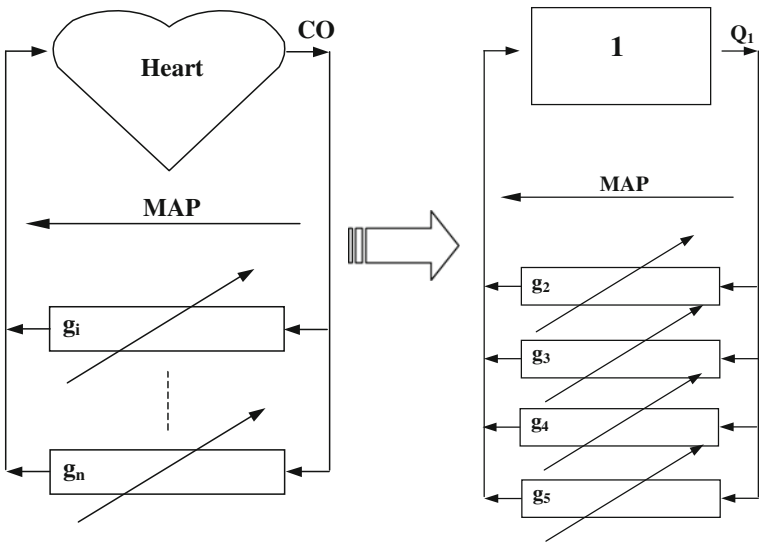

Fig. 2 Electrical analogy of the circulatory system [33] and its application in this study

this compartment is related to the central compartment, which is given by:

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

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.

2.1.3 Baroreflex

Yu et al. [32] described baroreflex as a set of transfer functions relating the mean arterial pressure to the maximum elastance, the systemic resistance, the heart rate and the unstressed ventricular volume as given by the following equation:

$$bfc = \frac{e^{c(MAP - MAP_0)}}{1 + e^{c(MAP - MAP_0)}}$$

where c is the empirical constant (mmHg). In this model, only maximum elastance and the systemic resistance are involved, and hence the baroreflex is limited to its action on them. The regulatory mechanism of the baroreflex may vary with the depth of anaesthesia and several other factors. However, the parameters involved in the transfer functions are assumed constant. The values of the parameters used in this model are summarized in Table 1 and are taken from [5, 11, 13, 31].

2.2 Model-based control

For designing the controllers, the model in the previous section was linearized at the nominal values of inputs: 0.6 vol% of isoflurane, 2 μg/kg/min of DP and 4 μg/kg/min of SNP to obtain a state–space model of the following form:

$$\begin{aligned} x_{t+1} &= Ax_t + Bu_t \\ y_t &= Cx_t + Du_t \end{aligned} \tag{1}$$

subject to the following constraints:

$$\begin{aligned} x_{min} \le x_t \le x_{max} \\ y_{min} \le y_t \le y_{max} \\ u_{min} \le u_t \le u_{max} \end{aligned} \tag{2}$$

where $x_t \in R^n$, $y_t \in R^l, u_t \in R^m$, are the state, output and input vectors, respectively, and the subscripts *min* and *max* denote lower and upper bounds, respectively; the corresponding values of outputs at the linearization point are: 57.38 mmHg of MAP, 61.1 BIS and 1.21 l/min of CO. Model predictive control [10] problem can then be posed as the following optimization problem:

$$\begin{aligned} \min_U J(U, x(t)) = {} & x_{t+N_y|t}^T P x_{t+N_y|t} \\ & + \sum_{k=0}^{N_y-1} \left[x_{t+k|t}^T Q x_{t+k|t} + u_{t+k}^T R u_{t+k} \right] \\ & s.t. x_{min} \le x_{t+k|t} \le x_{max}, k = 1, \ldots, N_c \\ & y_{min} \le y_{t+k|t} \le y_{max}, k = 1, \ldots, N_c \\ & u_{min} \le u_{t+k} \le u_{max}, k = 1, \ldots, N_c \\ & x_{t+k+1|t} = Ax_{t+k|t} + Bu_{t+k}, k \ge 0 \\ & y_{t+k|t} = Cx_{t+k} + Du_{t+k}, k \ge 0 \end{aligned} \tag{3}$$

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	g/ml
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	1/min
$g_{1,0}$	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	$cm^{7/2}\ g^{-1/2}$
MAP_0	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

where $U = \left[u_t^T, \ldots, u_{t+N_u-1}^T\right]^T$, Q and R are constant symmetric and positive definite matrices, P is given by the solution of the Riccati or Lyapunov equation, N_y, N_u and N_c are the prediction, control and constraint horizons, respectively, and the superscript T denotes transpose of the vector. Problem (3) is solved at the current time t for the current state x_t to obtain the vector of predicted state variables, $x_{t+1|t}, \ldots, x_{t+Ny|t}$ and the control actions $u_t, \ldots$, u_{t+Ny-1} are obtained. This linearized state–space form of the model is then adapted for designing MPC using the MATLAB [19].

The on-line computational requirements of MPC can be reduced to simple function evaluations by designing multi-parametric controllers [3, 6, 7, 21–25]. Multi-parametric controllers provide control variables as a set of explicit functions of the state variables, and the polyhedral regions in the space of the state variables where these functions are valid leading to much simpler implementation of the controller.

3 Results

3.1 Model validation

A number of dynamic simulations were performed using gPROMS [14] to validate the model proposed in Sect. 2.1. First, a simulation was carried out to see the effect of isoflurane on MAP and BIS. Figure 3a shows the profile of MAP when subjected to an uptake of 1 vol% of isoflurane. Figure 3b shows the drop in BIS when there is an uptake of 1 vol% of isoflurane, and then an increase in BIS at 1000 min when there is no uptake of isoflurane. It is observed that BIS drops to 40 for an isoflurane uptake of 1 vol%.

Another simulation was performed to see the effect on BIS when subjected to an uptake of 0.5 vol% of isoflurane. Figure 3c shows the performance where it is observed that BIS reaches a value of 65. General anaesthesia 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%.

In order to see the effect of dopamine on MAP, a simulation was performed, where the model was run at steady state for the first 10 min, then a drop of 20 mmHg in MAP was induced and finally 10 min after the drop, 5 μg/kg/min of dopamine was infused. Figure 4a shows that MAP decreases to 70 mmHg after the drop, and then increases to approximately 82 mmHg due to the baroreflex and then

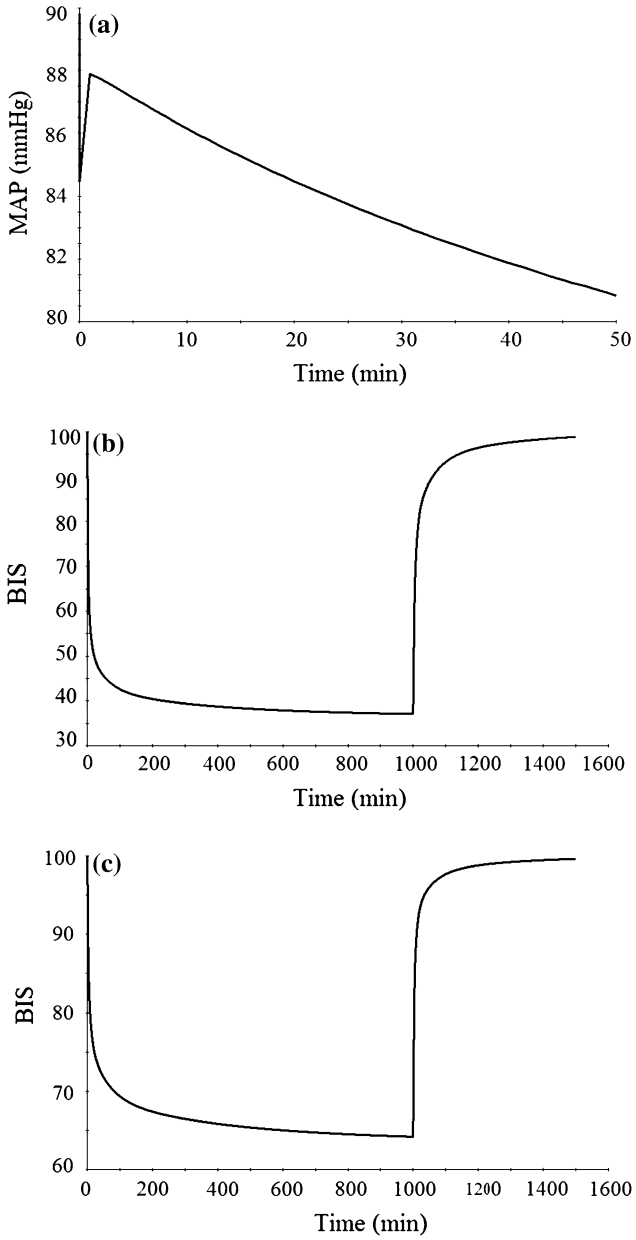

Fig. 3 Pharmacodynamic response to isoflurane infusion: **a** MAP response to an uptake of 1 vol% of isoflurane; **b** BIS response to an uptake of 1 vol% of isoflurane; and **c** BIS response to an uptake of 0.5 vol% of isoflurane

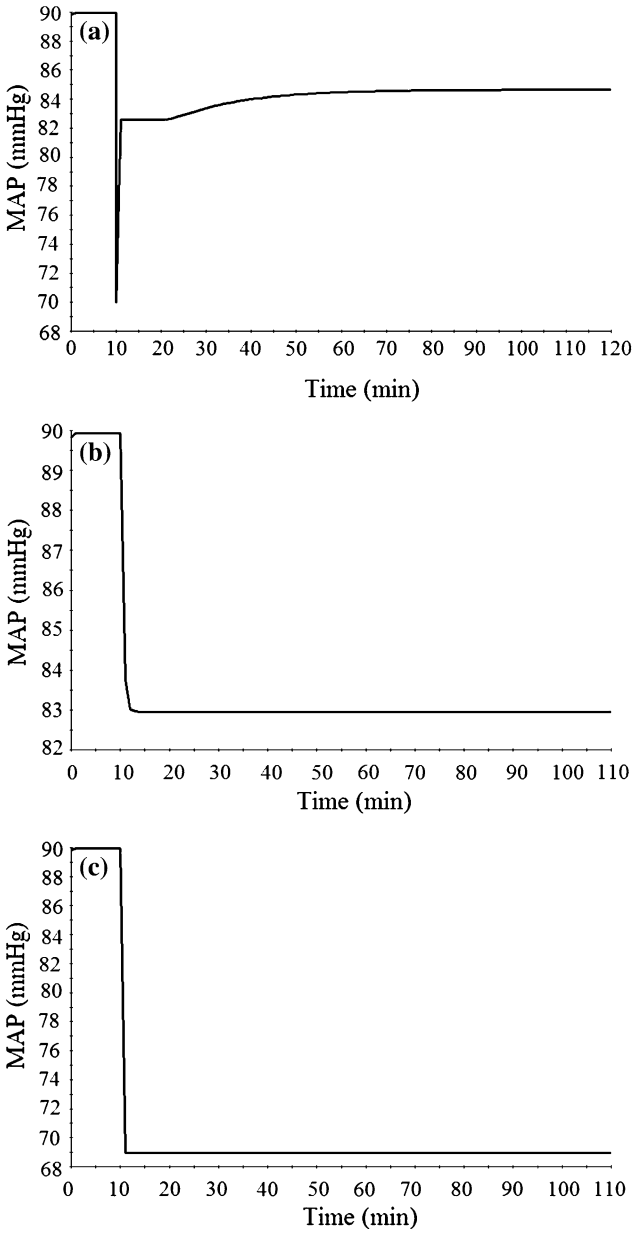

Fig. 4 MAP response: **a** DP infusion in response to a drop in MAP; **b** MAP response to a continuous injection of 1 μg/kg/min of SNP after 10 min; and **c** MAP response to a continuous injection of 10 μg/kg/min of SNP after 10 min

finally reaches the steady state after the infusion of dopamine.

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 (Fig. 4b) and 10 μg/kg/min of SNP decreases MAP to approximately 69 mmHg (Fig. 4c).

In order to validate the model's general behaviour, an anaesthetic procedure has been simulated, which consists of five parts. For the first 10 min, 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 anaesthetic state and lower the blood pressure to 60 mmHg. After 800 min, 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 min of the drop by giving an infusion of 4.5 μg/kg/min of DP to counteract the drop. Then after 60 min, MAP does not drop, and hence DP infusion was stopped. After another 40 min, the uptake of isoflurane and SNP was

stopped, and it was observed that the patient smoothly wakes up. Figure 5a and b shows the results of this simulation. It must be stressed that this procedure is oversimplified. First, the anaesthesiologist 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 subjected 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.

A number of dynamic simulation studies have been carried out to validate the applicability of the model to simultaneously regulate MAP, CO and hypnosis. The quantitative and qualitative trends of the plots presented in this section are similar to those observed in clinical trials [11, 12, 26].

3.2 Control of anaesthesia

As described in Sect. 2.2, the model was linearized and MPC problem was formulated. The model consists of 23 states, three outputs and three inputs. Figure 6a and b depict a comparison between the behaviour of two outputs (MAP and BIS) with respect to time in two different cases: when simulating the nonlinear model and the linearized one. It is apparent that there is a difference in behaviour between the two models, especially during the first period of simulation (0–50 min). It seems that the linearized model "overestimates" the Bispectral Index. However, the two models have the same steady behaviour, and their trends overlap after the first period of simulation. Similarly, in the case of MAP, there is some deviation initially, but the same trend is observed after a while.

For designing the MPC controller, the following constraints— input: $0 \leq DP \leq 7$ μg/kg *min*, $0 \leq SNP \leq 10$ μg/kg min, $0 \leq Isoflurane \leq 5$ vol%, and output: $40 \leq MAP \leq 150$ mmHg, $40 \leq BIS \leq 65$, $1 \leq CO \leq 6.5$ l/min—are used. A prediction horizon of 5, control horizon of 3 and sampling time of 0.5 min are considered. A set point of $[20\ -10\ 1]^{T}$ deviation from the nominal point of the output variables is given, and the performance of the controller is shown in Fig. 7. It is observed that the MPC tracks the set point quite well. From the above, it can be inferred that the model predictive control technology provides a promising platform for the automation of anaesthesia.

For the design of multi-parametric controller a reduced form of the model, corresponding to the infusion of isoflurane regulating MAP and BIS is considered. The model has seven states x_1-x_7, representing the concentration of

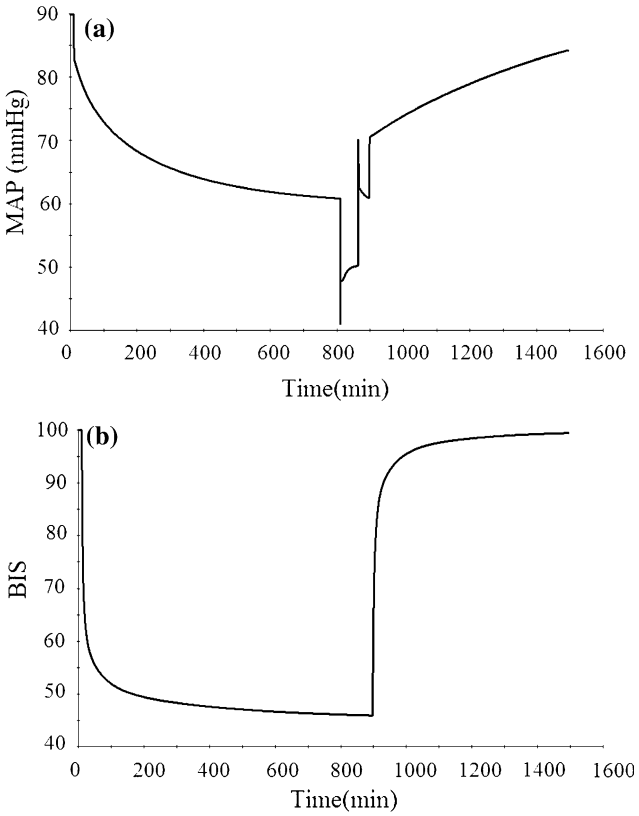

Fig. 5 Simulation of anaesthesia: **a** Simulation of the regulation of MAP during anaesthesia; and **b** Simulation of the regulation of BIS during anaesthesia

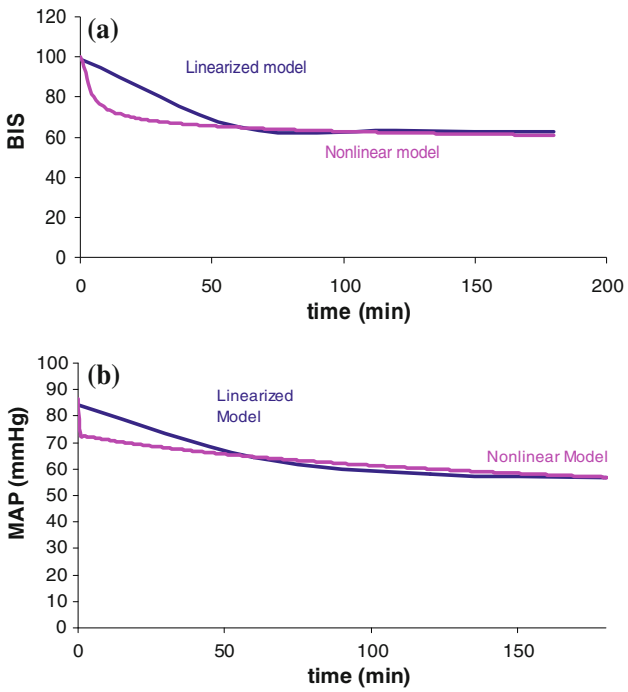

Fig. 6 Pharmacodynamic responses from linearized and nonlinear models: **a** Profile of BIS for linear and nonlinear models over time; and **b** Profile of MAP for linear and nonlinear model over time

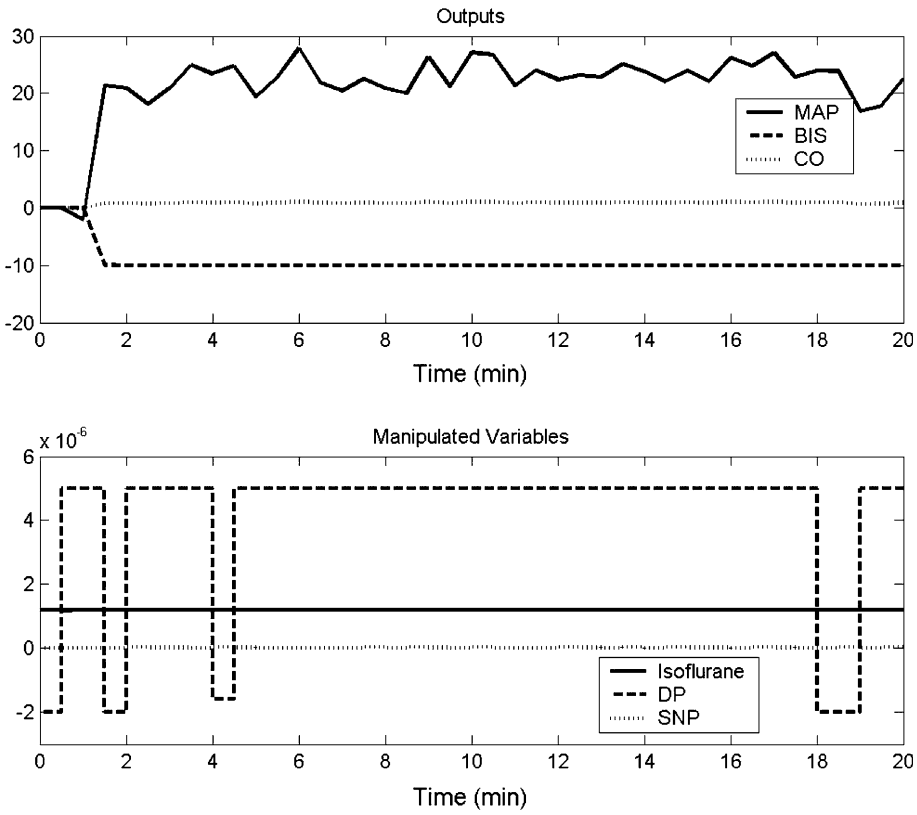

Fig. 7 MPC performance for anaesthesia

isoflurane in the five compartments and its effect on E_{max} and R_{sys} and the input variable is given by the inlet concentration of isoflurane. Prediction and control horizons of 3 and equal weightings on state and control variables are used resulting in 48 regions in the space of the state variables. The profile of the multi-parametric controller in one of the regions is given by$u = [-359.64\ -717.4\ -166.32\ -57.109\ -15.711\ -5.5925\ 0.77529]\ x + 0.077971$and the corresponding region by

$$\begin{bmatrix} -0.501 & -1 & -0.231 & -0.079 & -0.021 & -0.007 & 0.001 \\ 0.501 & 1 & 0.231 & 0.079 & 0.021 & 0.007 & -0.001 \\ 0.1853 & -1 & 0.085 & 0.210 & 0.100 & 0.027 & -0.002 \\ -0.057 & -1 & -0.026 & 0.238 & 0.335 & 0.130 & -0.014 \end{bmatrix}$$

$$x \leq \begin{bmatrix} 0.0000639 \\ 0.0000059 \\ -0.0000215 \\ -0.0003263 \end{bmatrix}$$

$$x_4, x_5 \geq 0$$

where x is the vector of deviation state variables. The performance of the multi-parametric controller was tested for a given input, and the profile of the state variables is shown in Fig. 8. It was observed that the profiles match closely with those obtained from the simulation of the nonlinear model by using gPROMS [14]. Uncertainty in model parameters due to inter- and intra-patient variability

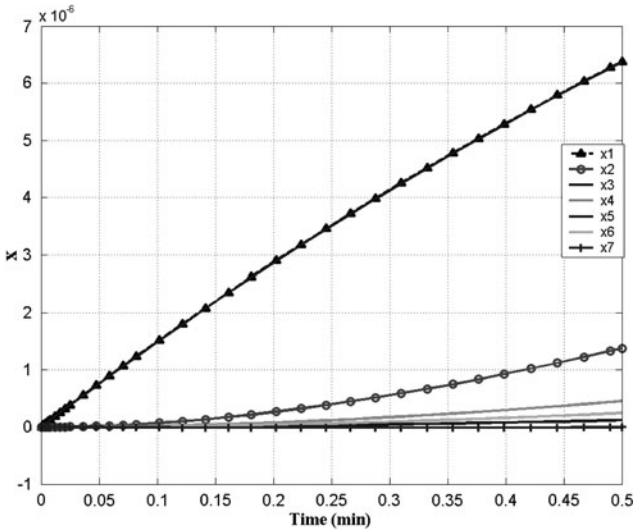

Fig. 8 Multi-parametric controller: state profiles

can be addressed using the robust MPC approach similar to that discussed for type 1 diabetes in Dua et al. [6], and the same will be addressed in future study.

4 Discussion

Automation of anaesthesia is expected to allow the anaesthesiologist 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 study, a compartmental model for anaesthesia, which takes into account simultaneous regulation of MAP and unconsciousness of the patients has been developed and validated. Model predictive and multi-parametric controllers were also derived, and a good controller performance was observed. This study paves the way for the development of advanced automation strategies for anaesthesia. The future study will involve deriving nonlinear multi-parametric controller to ensure a more robust controller implementation. Such an implementation will not rely on the online convergence of nonlinear programming solver, which is especially important when the model is non-convex. The developments based upon the derivation of the multi-parametric controller that were reported in this article can also be used by the anaesthesiologists to carry out "what-if" kind of analysis and failsafe analysis for various scenarios that may arise during the surgery. This can be achieved by simulating all the scenarios, corresponding to the polyhedral regions obtained for the multi-parametric controller. Execution of optimal drug infusion strategies and also reduction in the risks involved in surgery under anaesthesia are expected as a result of the proposed automation and implementation strategies. Further model validation, controller testing and exploring drug–drug interactions in an experimental setting will be addressed in future study.

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