

Model Based Parametric Control in Anesthesia

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Abstract

This work presents a compartmental model for delivery of three drugs (isoflurane, dopamine and sodium nitroprusside) for regulation of anesthesia. The key feature of this model is that mean arterial pressure, cardiac output and unconsciousness of the patient can be simultaneously regulated. This model is 'validated' by carrying out a number of dynamic state simulations and then used for designing model based parametric controllers.

Keywords: Anesthesia, Mean Arterial Pressure, Model Based Control, Parametric Controller

1. Introduction

Safe and adequate anesthesia is characterized by muscle relaxation, hypnosis and analgesia while maintaining vital functions such as mean arterial pressure (MAP), heart rate and cardiac output (CO) within certain desired ranges. A tight control of these vital functions is very important; otherwise it may lead to fatal situations. The anesthesiologist maintains these vital functions by regularly infusing various anesthetic drugs and/or intravenous fluids. Automatic control of the vital functions can reduce undesirable situations and improve the safety of the patient, by monitoring conditions that can not be measured easily, allowing the anesthesiologist to focus on critical issues, and also reduce the cost of the drugs and the time spent in the post-operative care unit. The automatic control techniques rely on a model of the patient that can incorporate the dynamic response of the patient to drug infusions and disturbances (Yasuda *et al.*, 1991; Rao *et al.*, 2001; Mahfouf *et al.*, 2003). Gentilini *et al.* (2001) observed that controlling MAP and hypnosis simultaneously with isoflurane was difficult. Yu *et al.* (1990) proposed a model for regulating MAP and CO using dopamine (DP) and sodium nitroprusside (SNP), but the control of hypnosis was not considered.

In the next section, a compartmental model is presented, which allows the simultaneous regulation of the MAP, CO and the unconsciousness of the patients. The model is characterized by: (i) pharmacokinetics for the uptake and distribution of the drugs, (ii)

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pharmacodynamics which describes the effect of the drugs on the vital functions and (iii) baroreflex 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. In Section 3 model based controllers for the regulation of anesthesia are designed by using Model Predictive Control (MPC) Toolbox (1998). Note that MPC solves a quadratic program at regular time intervals. Pistikopoulos *et al.* (2002), have presented model based parametric controllers that partition the space of state variables into a number of regions and each region is characterized by a control law, which is an explicit function of the state variables. This parametric control technology is used to design an explicit controller for the infusion of isoflurane for regulation of MAP and BIS. This reduces implementation of model based controllers to simple function evaluations. Concluding remarks are presented in Section 4.

2. Modelling Anesthesia

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

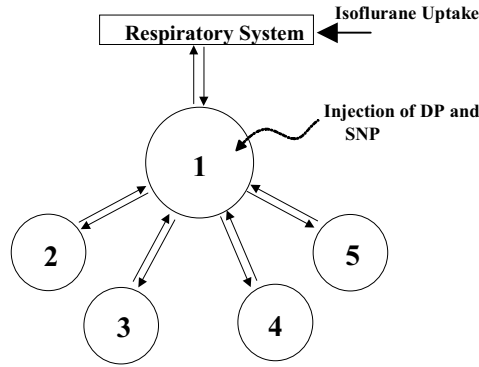


Figure 1. Compartmental Model

The compartments 1-5 represent Lungs, Vessel rich organs (e.g. liver), Muscles, Other organs and tissues and Fat tissues respectively. The distribution of the drugs occurs from the central compartment to the peripheral compartments by the arteries and from the peripheral to the central by the veins. The first compartment in Figure 1 is the central compartment and heart can be considered to be belonging to the central compartment, whereas compartments 2-5 are the peripheral compartments.

2.1 Pharmacokinetic Modelling

The pharmacokinetic model is developed based on the works of Yasuda *et al.* (1991), Yu *et al.* (1990) and Gentilini *et al.* (2001). The uptake of isoflurane in central compartment via the respiratory system is modelled as:

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

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 is 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). For the central compartment, the concentration of isoflurane is given by:

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

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). The concentration of DP and SNP in the central compartment is modelled as follows:

$$V_1 \frac{dC_1}{dt} = \sum_{i=2}^5 \left(Q_i \left(\frac{C_i}{R_i} - C_1 \right) \right) + C_{inf} - \frac{1}{\tau_{1/2}} C_1 V_1 \quad (3)$$

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). The distribution of isoflurane in compartments 2 to 5 is given by

$$V_i \frac{dC_i}{dt} = Q_i \left(C_1 - \frac{C_i}{R_i} \right) - k_i C_i, \quad i = 2, \dots, 5 \quad (4)$$

The natural decay of DP and SNP in the body, for compartment 2 to 5, is given by:

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

2.2 Pharmacodynamic Modelling

DP and SNP affect MAP indirectly. These drugs influence two of the heart's characteristic parameters: maximum elastance (E_{max}) and systemic resistance (R_{sys}), which is given by:

$$\frac{dEff}{dt} = k_1 C_1^N (Eff_{max} - Eff) - k_2 Eff \quad (6)$$

where Eff is the measure of the effect of drug on the parameters of interest, $E_{max} = E_{max,0} (1 + Eff_{DP} - E_{max})$, $R_{sys} = R_{sys,0} (1 - Eff_{DP} - R_{sys} - Eff_{SNP} - R_{sys})$, 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:

$$MAP^2 \frac{1}{R_{sys}^2} + 2K^2 MAP - 2K^2 V_{LV} E_{max} = 0 \quad (7)$$

The relationship between MAP and CO is given by:

$$MAP = R_{sys} \times CO \quad (8)$$

where MAP is the mean arterial pressure (mmHg) and CO is cardiac output (L/min).

Isoflurane affects MAP as follows:

$$MAP = \frac{Q_1}{\sum_{i=2}^5 (g_{i,0} (1 + b_i C_i))} \quad (9)$$

where, $g_{i,0}$ is the baseline conductivities (mL/(min.mmHg)) and b_i is the variation coefficient of conductivity (mL/g). There is experimental evidence that a transportation delay exists between the lungs and the site of effect of isoflurane on the unconsciousness of the patient. In order 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:

$$\frac{dC_e}{dt} = k_{e0} (C_1 - C_e) \quad (10)$$

where C_e is the concentration of isoflurane in the effect compartment (g/mL), and k_{e0} is the kinetics in the effect compartment (min^{-1}). The action of isoflurane can be then expressed as follows:

$$\Delta BIS = \Delta BIS_{MAX} \frac{C_e^\gamma}{C_e^\gamma + EC_{50}^\gamma} \quad (11)$$

where $\Delta BIS = BIS - BIS_0$, $\Delta BIS_{MAX} = BIS_{MAX} - BIS_0$, BIS_0 is the baseline value of BIS (assumed to be 100), BIS_{MAX} is the maximum 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

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:

$$bfc = \frac{e^{c(MAP - MAP_0)}}{1 + e^{c(MAP - MAP_0)}} \quad (12)$$

where c is the empirical constant (mmHg).

For further details on the model and the parameters used see Dua *et al.*, 2005.

3. Control of Anesthesia

The model presented in the previous section was validated by carrying out a number of dynamic simulations for different amounts of drug dosages and disturbances using gPROMS (2003). This model was then used for designing model based and parametric controllers. For designing model based controllers, the model was linearized at the nominal values of inputs: 0.6% vol. of isoflurane, 2 $\mu\text{g/kg/min}$ of DP and 4 $\mu\text{g/kg/min}$ of SNP and outputs: 57.38 mmHg of MAP, 61.1 BIS and 1.21 L/min of CO to obtain a state-space model consisting of 23 states, 3 outputs and 3 inputs. This state-space form of the model is then adapted for designing model predictive controller by using the MATLAB Model Predictive Control Toolbox (1998). For designing the MPC controller, the following input: $0 \leq DP \leq 7 \mu\text{g/kg.min}$, $0 \leq SNP \leq 10 \mu\text{g/kg.min}$, $0 \leq$

Isoflurane $\leq 5\%$ vol., and output constraints: $40 \leq MAP \leq 150$ 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 minutes 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 Figure 2 where the control variables are also deviations from the nominal values. It is observed that the MPC tracks the set point quite well.

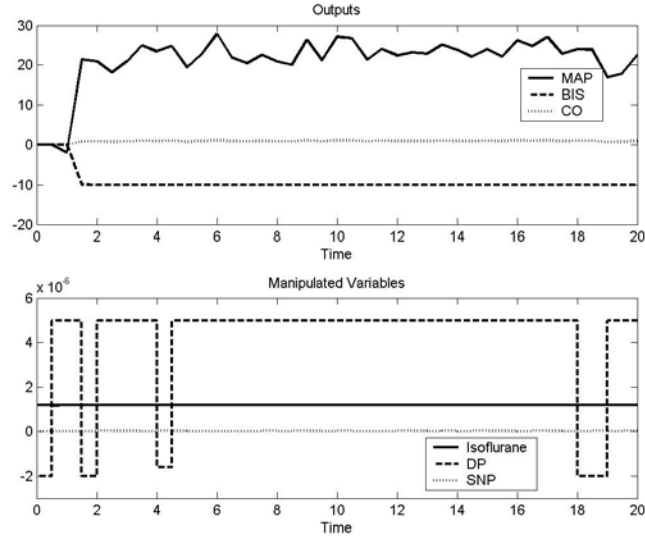


Figure 2. MPC Performance for Anesthesia

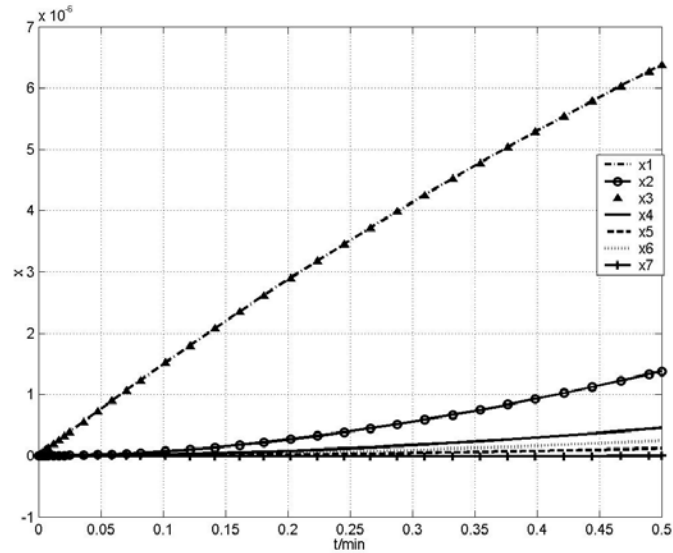


Figure 3. Parametric Controller: State Profiles

For the design of parametric controller (Pistikopoulos *et al.*, 2002) a reduced form of the model, presented in section 2, corresponding to the infusion of isoflurane regulating MAP and BIS is considered. The model has 7 states, x_1 to x_7 , representing the concentration of isoflurane in the 5 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 performance of the parametric controller was tested for a given input and the profile of the state variables is shown in Figure 3. It was observed that the profiles match closely with those obtained from the simulation of the nonlinear model by using gPROMS.

4. Concluding Remarks

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 three drugs for the simultaneous regulation of mean arterial pressure and unconsciousness of the patient has been presented. This model was validated and then used for designing model based and parametric controllers. The performance of the controllers was tested and observed to be very good. From the results obtained it can be inferred that the model based and parametric control are promising technologies for automatic control of MAP, CO and unconsciousness of the patients being operated under anesthesia.

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