PHYSIOLOGICAL MODELLING AND FUZZY CONTROL OF ANAESTHESIA VIA VAPORISATION OF ISOFLURANE BY LIQUID INFUSION

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Abstract: The paper reports on the development and simulation of a physiological model relating to Depth of Anaesthesia via Mean Arterial Pressure (MAP) measurements using the anaesthetic drug isoflurane. Isoflurane is an anaesthetic gas normally administered through a vaporiser-based system which was widely reported to be unreliable and unsuitable for precision driving. Hence, in this study we propose a new technique which allows such anaesthetic to be administered first as a liquid solution which is later vaporised as it is passed through a heating chamber; such effect being included in the overall model structure. Moreover, the development and application of a fuzzy constrained Single Input Single Output (SISO) version of the popular Generalised Predictive Control (GPC) algorithm, which uses the Quadratic programming (QP) approach, is presented; Mean Arterial pressure (MAP) is used as an inferential variable to indicate the level of unconsciousness. Simulation experiments showed that excellent regulation of blood pressure around set-point targets is achieved.

Keywords: Anaesthesia, physiology, modelling, predictive control, simulation, real-time.

1. INTRODUCTION

Anaesthesia is generally described as that part of the medical profession which ensures that the patient's body remains insensitive to pain an other stimuli during surgical operations. It includes muscle relaxation (paralysis), unconsciousness, and analgesia (pain relief). In contrast to muscle relaxation, depth of anaesthesia is more difficult to quantify accurately. It is in fact agreed that there is no absolute standard for the definition of clinical state of anaesthesia against which new methods designed to measure 'depth' of anaesthesia can be proposed (Robb *et al*, 1988). Thus, one approach has been to merge a number of clinical signs and on-line monitored data to produce an expert system adviser for the anaesthetist. In spite of the multi-sensor nature of the above approach, it appears that, during the majority of operating periods when no emergency conditions occur, a good indication of unconsciousness can be obtained from a single on-line monitored variable. Thus, the use of arterial blood pressure, monitored via an inflatable cuff using a Dinamap instrument, has been investigated for feedback control with simple PI strategies (Robb *et al*, 1988). In this case, the control actuation was via a stepper motor driving the dial on a gas vaporiser. This concept forms the basis for the modelling and control aspects of unconsciousness in the following work. In particular, we have focused on the drug isoflurane in these studies, it being commonly used in modern surgery.

The control theme at the heart of this study is that of Model-Based Predictive Control, particularly Generalised Predictive Control (GPC) (Clarke *et al*, 1987). This strategy is seen by many as the control strategy that had the most significant impact on solving complex industrial problems, including those within the realm of biomedicine (Mahfouf and Linkens, 1998). In this paper hard constraints are introduced as part of the optimisation problem and the CARIMA[1] model,

[1] Controlled Auto-Regressive Integrated Moving Average

normally used in the standard GPC algorithm, is extended to include a fuzzy modelling approach via the Takagi-Sugeno-Kang model (Takagi and Sugeno, 1985), but in the CARIMA sense. Hence, this paper is organised as follows: Section 2 will review the re-circulatory physiological model relating to the drug isoflurane (Zwart *et al, 1972*), together with our own modification in terms of the modelling of the liquid anaesthetic. In Section 3, the development of constrained GPC but using the fuzzy modelling approach is briefly reviewed, while in Section 4 results of the simulation experiments are presented and discussed. In Section 5 the transfer of the overall control system to the operating theatre is described and briefly discussed. Finally, in Section 6 conclusions relating to this study together with plans for the future are given.

2. THE ANAESTHESIA MODEL RELATING TO LIQUID ISOFLURANE

The model structure which was first introduced by Zwart and his co-workers (1972) and later exploited by Derighetti (1999), is shown in Figure 1. It consists of two parts; one part for the uptake and distribution of drugs, and the other part for the circulation of the blood-flows. The overall non-linear model associated with the anaesthetic describes such pharmacokinetics (uptake and distribution) of the drug, the circulation model (blood flow), as well as pharmacodynamics (effects of the drugs on the patient's body) as follows:

The state vector $p(t)$ describes the partial pressure of the anaesthetic gas in every compartment. The input to the system being the concentration of the anaesthetic gas in the inspired air (p_{Air}), v refers to 'venous', A refers to "Artery", and L refers to "Lungs", $g_{j,0}$, b_i, k_i, CO_0, and λ_i are all terms which can be inferred from the partial pressures or are constants which are either patient or drug dependent (Derighetti, 1999). The Mean Arterial Pressure (MAP) is given by the following equation:

$$\begin{cases} \dot{p}_i = k_i g_{i,0} CO_0 (1 + a_1 p_1 + a_2 p_2 + a_A p_A)(p_A - p_i) \dfrac{1 + b_i p_i}{\sum_{j=1}^{9} g_{j,0}(1 + b_j p_j)} \\ \dot{p}_L = k_L \{\lambda_b (1 - l_s) CO_0 (1 + a_1 p_1 + a_2 p_2 + a_A p_A)(p_V - p_L) + q_{Air}(p_{Air} - p_L)\} \\ \dot{p}_A = k_A CO_0 (1 + a_1 p_1 + a_2 p_2 + a_A p_A)[p_V l_s + p_L (1 - l_s) - p_A] \\ \dot{p}_V = k_V CO_0 (1 + a_1 p_1 + a_2 p_2 + a_A p_A) \left[\dfrac{\sum_{i=1}^{9} g_{i,0}(1 + b_i p_i) p_i}{\sum_{j=1}^{9} g_{j,0}(1 + b_j p_j)} - p_V \right] \end{cases} \quad (1)$$

and finally,

$$MAP = CO_0 \frac{1 + a_1 p_1 + a_2 p_2 + a_3 p_A}{\sum_{j=1}^{9} g_{j,0}(1 + b_j p_j)} \quad (2)$$

where CO_0 is the total cardiac output prior to any anaesthetic being given.

Because giving 100% O_2 can cause the patient to have lung problems, a mixture of 70% N_2O and 30% O_2 is preferred during anaesthesia which is generally seen as a good compromise between a fast reaction to the anaesthetic and pollution of the operating theatre with gas. Because N_2O has a mild anaesthetic effect it acts as a carrier for isoflurane and lowers the drug equilibrium-time. Hence, its effect was modelled by increasing the effective air-flow q_{Air} in Equation (1) to take into account the partial pressures in relation to this gas (Derighetti, 1999). Hence, the following modified expression for air-flow q_{Air} is used:

$$\begin{aligned} q_{Air_{new}} &= q_{Air}(1 + K_{q_{Air}}) \\ K_{q_{Air}} &= 0.235 \end{aligned} \quad (3)$$

It is widely recognised that the use of a continuous infusion pump provides a smoother method of controlling the anaesthetic agent concentration in comparison to a vaporiser. Hence, we adopted a more recent technique which consists of delivering the anaesthetic in a liquid form then transformed into a gas as it passes through a heating chamber, this having also the advantage of avoiding to drive a vaporiser with all its software complexity (Mahfouf *et al*, 1997). In order to reflect such a modification, a model which describes the dynamics associated with the vaporisation process, was elicited through an

experimental study using the following first-order differential equation:

$$\dot{p}_{iso\_gas} = -k_{1g} q_{Air} p_{iso\_gas} + k_{2g} q_{iso\_liq} \qquad (4)$$

where p_{iso_gas}, p_{iso_liq} are the concentrations of the anaesthetic in "gas" and "liquid" forms respectively, and k_{1g}, k_{2g} are constants which we have determined experimentally as being (for a 2 litres per hour volume of fresh air):

$$k_{1g} = 0.22$$
$$k_{2g} = 3.40$$

Hence, Equation (4) can be written as follows:

$$\frac{Iso\_Gas}{Iso\_Liquid} = \frac{3.4}{1 + 0.44s} \qquad (5)$$

The model described by Equations (1-5) is represented via a SIMULINK diagram as shown in Figure 2. Figures 3a, b, and c show the results of an open-loop study in which a continuous infusion of 70 ml/hr of liquid isoflurane was initiated for a period of 200 minutes. The level of blood pressure dropped from a baseline of 90 mmHg to 45 mmHg which later rose to 83 mmHg after isoflurane was switched-off indicating the nonlinear behaviour of this variable.

This model will form the basis for a closed-loop control strategy design using the theme of constrained fuzzy model-based predictive control as will be outlined in the next section.

3. CONSTRAINED GENERALISED PREDICTIVE CONTROL

3.1 Controller Formulation

The long-range predictive controller developed in this research study is based on the Popular Generalised Predictive Control (GPC) strategy (Clarke *et al*, 1987) whose theoretical background is briefly reviewed here:

Consider the following locally linearised discrete model in the backward shift operator z^{-1}:

$$A(z^{-1})\Delta y(t) = B(z^{-1})\Delta u(t-1) + C(z^{-1})\zeta(t) \quad (6)$$

where:

$$A(z^{-1}) = 1 + a_1 z^{-1} + a_2 z^{-2} + \ldots + a_{n_a} z^{-n}$$
$$B(z^{-1}) = b_1 + b_2 z^{-1} + b_3 z^{-2} + \ldots + b_{n_b} z^{-m+1}$$
$$C(z^{-1}) = c_0 + c_1 z^{-1} + c_2 z^{-2} + \ldots + c_p z^{-p}$$
$$\zeta(t) \text{ is an uncorrelated random sequence.}$$
$$\Delta = 1 - z^{-1}$$

$u(t)$ represents the control input and $y(t)$ is the measured variable. The controller computes the vector of controls using optimisation of a function of the form:

$$J_{GPC} = \sum_{j=N_1}^{N_2} \left[(P(z^{-1})\,\hat{y}(t+j) - \omega(t+j))^2 \right] + \sum_{j=1}^{NU} \left[\lambda(j)(\Delta u(t+j-1))^2 \right] \qquad (7)$$

where N_1 is the minimum costing (output) horizon, N_2 is the maximum costing horizon, NU is the control horizon, ω is the future set-point, $\lambda(j)$ is the control weighting sequence, and $P(z^{-1})$ is the inverse model in the model-following context with $P(1) = 1$. Furthermore, the $C(z^{-1})$ polynomial in Equation (4) is replaced by a fixed polynomial $T(z^{-1})$ known as the observer polynomial for the predictions $P(z^{-1})\,\hat{y}(t+j)$. This as already mentioned, enables an offset of the effect of the Δ operator as a high-pass filter on the input-output data.

When the control horizon NU ,which reflects the number of degrees of freedom for the controller, is greater than 1, the solution of (7) in the **unconstrained** case (physical and terminal constraints not included prior to optimisation), differs from that in the **constrained** case (physical and terminal constraints included before optimisation takes place). In the latter case the final solution can be found in the 'optimal' sense. Hence, one way of solving (7) in the constrained case is to consider the following Least Squares Inequality (LSI) problem (Mahfouf and Linkens, 1998):

Minimise $\|Ax - b\|$ subject to $Hx > h$ (8)

Where x is the NU solution vector, H is the static/dynamic constraints information matrix and h is a vector containing the lower and upper limits of the constraints. In the case of Equation (7), we have:

$$A = \begin{bmatrix} G_d \\ \lambda^{1/2} \end{bmatrix}; \quad b = \begin{bmatrix} \omega - P.\hat{y} \\ 0 \end{bmatrix}$$

H and h will depend on the types of constraints which are considered, i.e. input rate constraints, input magnitude constraints and output magnitude constraints. If all three types of constraints are considered, then we would write the conditions as follows:

$$\begin{cases} \Delta u_{\min} \le \Delta u(t+j-1) \le \Delta u_{\max} \\ u_{\min} \le u \le u_{\max} \\ \Phi_{\min} \le \Phi(t+j) \le \Phi_{\max} \end{cases} \tag{9}$$

where $\Delta u_{\min}$, $\Delta u_{\max}$, $u_{\min}$, $u_{\max}$, $\Phi_{\min}$, and $\Phi_{\max}$ are the minimum and maximum allowed control increments, absolute control moves, and the outputs respectively. It is worth noting that the Quadratic Programming (QP) problem can be solved using the method proposed by Lawson and Hanson (1974). Also, when using both input and output constraints simultaneously **infeasibility** problems may be encountered (when the optimiser cannot satisfy all constraints at once). Several methods can be used to circumvent such a problem, but the one we used in this instance is the hierarchical removal of output constraints starting from the bottom predictions until the optimiser is capable of returning a **feasible** solution (Mahfouf and Linkens, 1998).

3.2 Fuzzy Process Model

One common denominator of all Model Based Predictive Control (MBPC) strategies which represents their *"raison d'etre"* is their assumption of a model which has to be quite accurate. The modelling of real world systems, however, often presents problems. As processes increase in complexity, they become less amenable to direct mathematical modelling based on physical laws since they may be distributed, stochastic, non-linear and time-varying, uncertain, etc. According to Zadeh's Principle of Incompatibility (Zadeh, 1973), the closer one looks at a real world problem, the fuzzier becomes the solution. Hence, the modelling problem, instead of being posed within a strictly analytical framework, is based on empirically acquired knowledge regarding the operation of the process.

Many fuzzy modelling methods have been proposed in the literature. Most are based on collections of fuzzy *IF-THEN* rules of the following form:

$$IF\ x_1\ is\ B^1\ and \ldots and\ x_n\ is\ B^n\ THEN\ y\ is\ C \tag{10}$$

where $\underline{x} = (x_1, \ldots, x_n)^T$ and y are the input and output linguistic variables respectively, and B^i and C are linguistic values characterised using membership functions. It is considered that this fuzzy rule representation provides a convenient framework to incorporate human experts' knowledge

An alternative method of expressing fuzzy rules proposed by Takagi and Sugeno (1985) has fuzzy sets only in the premise part and a regression[2] model as the conclusion:

$$\begin{aligned} &IF\ x_1\ is\ B^1\ and \ldots and\ x_n\ is\ B^n \\ &THEN\ \ y = c_0 + c_1 x_1 + \cdots + c_n x_n \end{aligned} \tag{11}$$

where $\underline{x}$, y and B^i are defined as above, and c_i are real-valued parameters.

Consider a single input single output (SISO) system which can be modelled using the method proposed by Takagi and Sugeno. Assuming that the input space is partitioned using p fuzzy partitions and that the system can be represented by fuzzy implications (one in each fuzzy sub-space), we can write the following implication L:

$$\begin{aligned} &L^i : IF\ y(t)\ is\ B^i\ THEN\ y_m(t+1) = a_1^i y(t) + \cdots \\ &+ a_j^i y(t-j+1) + b_1^i u(t) + \cdots + b_l^i u(t-l+1) + k_i \end{aligned} \tag{12}$$

Such model representation in the consequent part of the above implication is called a Auto-regressive Moving Average (ARMAX) model.

[2] This model can be either linear or non-linear.

Several linear adaptive predictive controllers have been designed using such model representation, however, the most popular linear model structure is the so-called CARIMA structure which was found to be effective against offsets which can be present in the data. Using a CARIMA model structure, the fuzzy implication (10) can be written as follows:

$$L^i : IF\ y(t)\ is\ B^i\ THEN\ \Delta y_m(t+1) = -a_1^i \Delta y(t) - \cdots - a_j^i \Delta y(t-n_a+1) + b_1^i \Delta u(t) + \cdots + b_l^i \Delta u(t-n_b+1) \quad (13)$$

The model parameters can be expressed in the following matrix form:

$$\Theta = \begin{bmatrix} a_1{}^1 \ldots a_{n_a}{}^1 & b_1{}^1 \ldots b_{n_b}{}^1 \\ \vdots & \vdots \\ a_1{}^p \ldots a_{n_a}{}^p & b_1{}^p \ldots b_{n_b}{}^p \end{bmatrix}$$

The overall fuzzy model output (in incremental form) can be written as follows:

$$\Delta y_m(t+1) = \beta\ \Theta\ \Phi(t) \quad (14)$$

where,

$$\Phi(t) = \begin{bmatrix} -\Delta y(t),\ -\Delta y(t-1), \cdots, \\ -\Delta y(t-n_a+1), \Delta u(t), \Delta u(t-1), \cdots, \\ \Delta u(t-n_b+1) \end{bmatrix}^T$$

$$\beta = \lfloor \beta_1\ \beta_2 \cdots \beta_i \cdots \beta_p \rfloor$$

and,

$$\beta_i = \frac{B^i[y(t)]}{\sum_{i=1}^{p} B^i[y(t)]} \quad (15)$$

$B^i[y(t)]$ is the grade of membership of $y(t)$ in B^i and β is a vector of the weights assigned to each of the p implications at each sampling instant.

4. SIMULATION RESULTS

The simulation study considered the continuous non-linear system (1-5) which was represented in MATLAB-SIMULINK, using a sampling interval of 1 minute, while the external constrained predictive control module was coded in 'C'. For parameter estimation, a UD-factorisation method was used on incremental data. At time $t = 0$ an initial arterial pressure of $MAP_0 = 90$ mmHg was assumed. The set-point command was 70 mmHg then 80 mmHg for a 400-minute total simulation time. The GPC algorithm used a combination of tuning factors of (1, 8, 2, 0) for (N_1, N_2, NU, λ) together with a filter polynomial $T(z^{-1}) = (1 - 0.8z^{-1})^2$. Different fuzzy partitions of the input space can be used; we chose triangular shapes for simplicity (see Figure 4).

The algorithm used the three types of constraints with the following limits:

$$\begin{aligned} &-0.2 \le \Delta u(t+j-1) \le 0.2 \\ &0 \le u(t+j-1) \le 5 \\ &\omega - 5 \le \Phi(t+j) \le \omega + 5 \\ &j = 1, \ldots, NU \end{aligned} \quad (16)$$

In the first experiment (an air-flow of 2 litres per hour was used throughout), a fuzzy model with 2 partitions was used and the output obtained was that shown in Figure 5 where it can be seen that tracking was good without too much compromise on the control activity which remained reasonable. This is in contrast to Figure 6 which corresponds to the application of the unconstrained GPC algorithm where, although the output tracking was good, the control activity was too high; in anaesthesia terms the patient would be consuming an unnecessarily high dose of isoflurane which, apart from not being cost-effective, can delay the patient's recovery from anaesthesia significantly.

It is worth noting that this simulation study and others (not reported here) formed the basis for the transfer of the overall closed-loop control system to the operating theatre for administration of isoflurane during surgery as the next Section explains.

5. REAL-TIME SET-UP

The real-time closed-loop control system which was transferred to the operating theatre is shown in Figure 7 and comprises:

- An IBM compatible microcomputer which incorporates the control system.
- A Braun Perfusor Secura digital pump driving a disposable syringe containing a liquid solution of isoflurane.
- A Dinamap Instrument for measuring the arterial blood pressure.
- A Capnomac Ultima Device for measuring the inspired and expired isoflurane concentrations.

The links between the syringe pump, the Capnomac machine, the blood pressure monitor, and the computer are via three RS-232 serial ports.

Such closed-loop system is in the process of being applied in theatre after having undergone the most rigorous tests in terms of reliability and also safety to gain the approval of the relevant Ethics Committee at the Western Infirmary in Glasgow.

6. CONCLUSIONS

A new algorithm, which combines the advantages of model-based predictive control, particularly GPC in terms of constraints, and fuzzy systems, which allows the absorption of model uncertainties, has been proposed for the control of unconsciousness via blood pressure measurements. First, a simulation platform was built around a non-linear recirculatory physiological model which was modified to include a more efficient way of delivering the anaesthetic in a liquid form rather than gas. The simulation results showed that the fuzzy-based constrained algorithm was effective in terms of set-point tracking and drug consumption. It is hoped that the constrained version of the algorithm will be tested in a series of trials and that the control system is extended to include an inner loop which will take into account the true inspired concentration of isoflurane.

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8. ACKNOWLEDGEMENT

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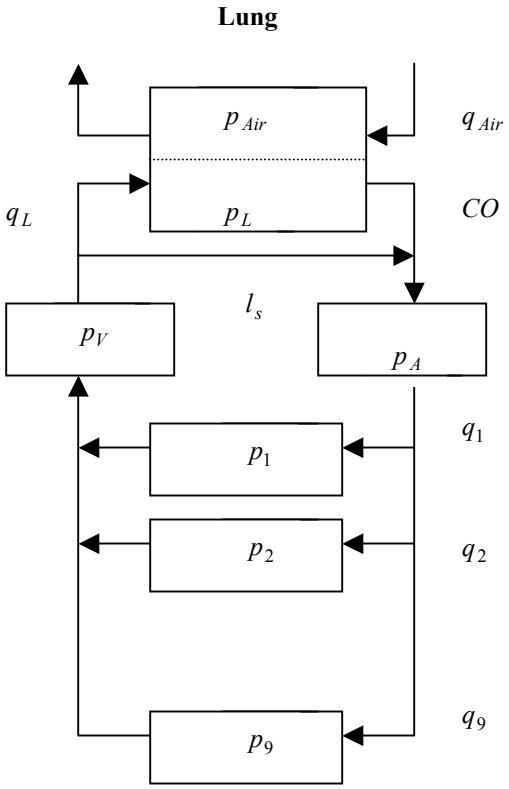

Figure 1 The patient physiological model relating to inhalational anaesthesia (Zwart *et al*, 1972).

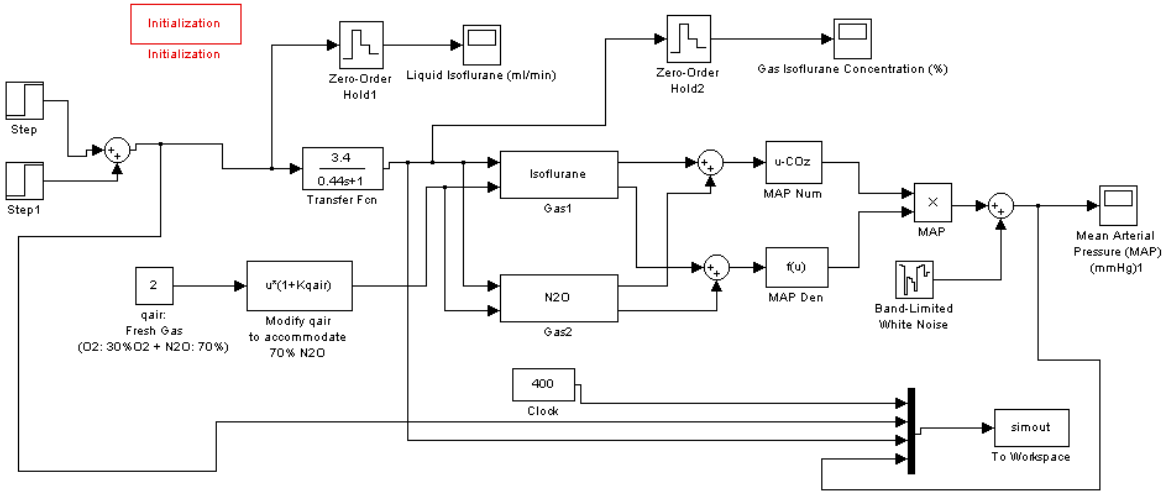

Figure 2 A SIMULINK representation of the anaesthesia model relating to isoflurane

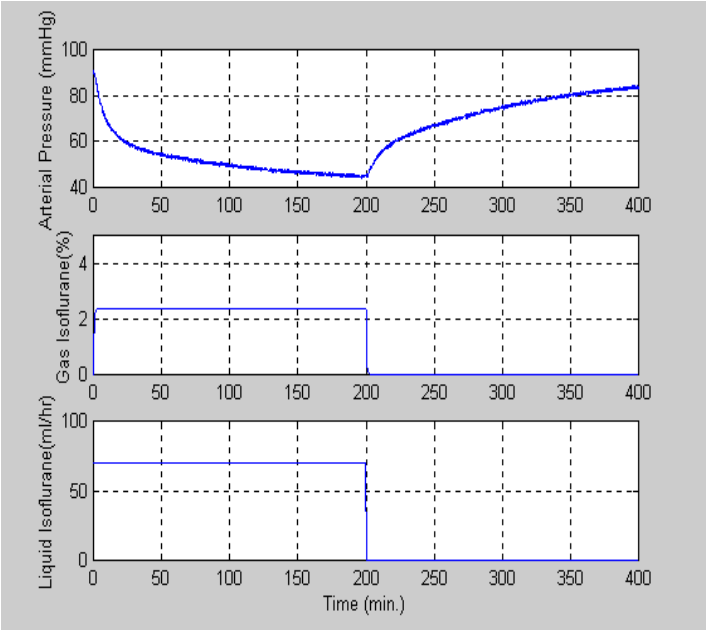

Figure 3 Patient physiological model relating to inhalational anaesthesia.

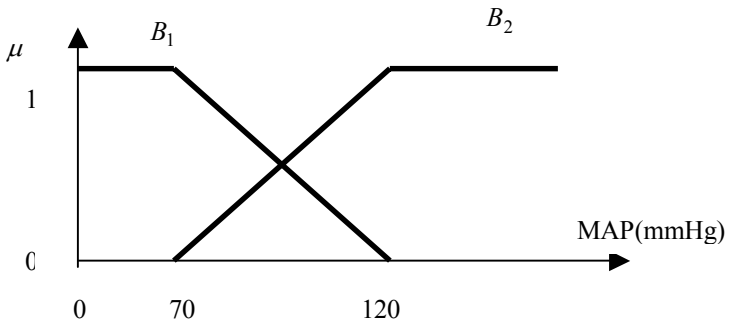

Figure 4 A 2-partition fuzzy representation of the input space using triangular membership Functions.

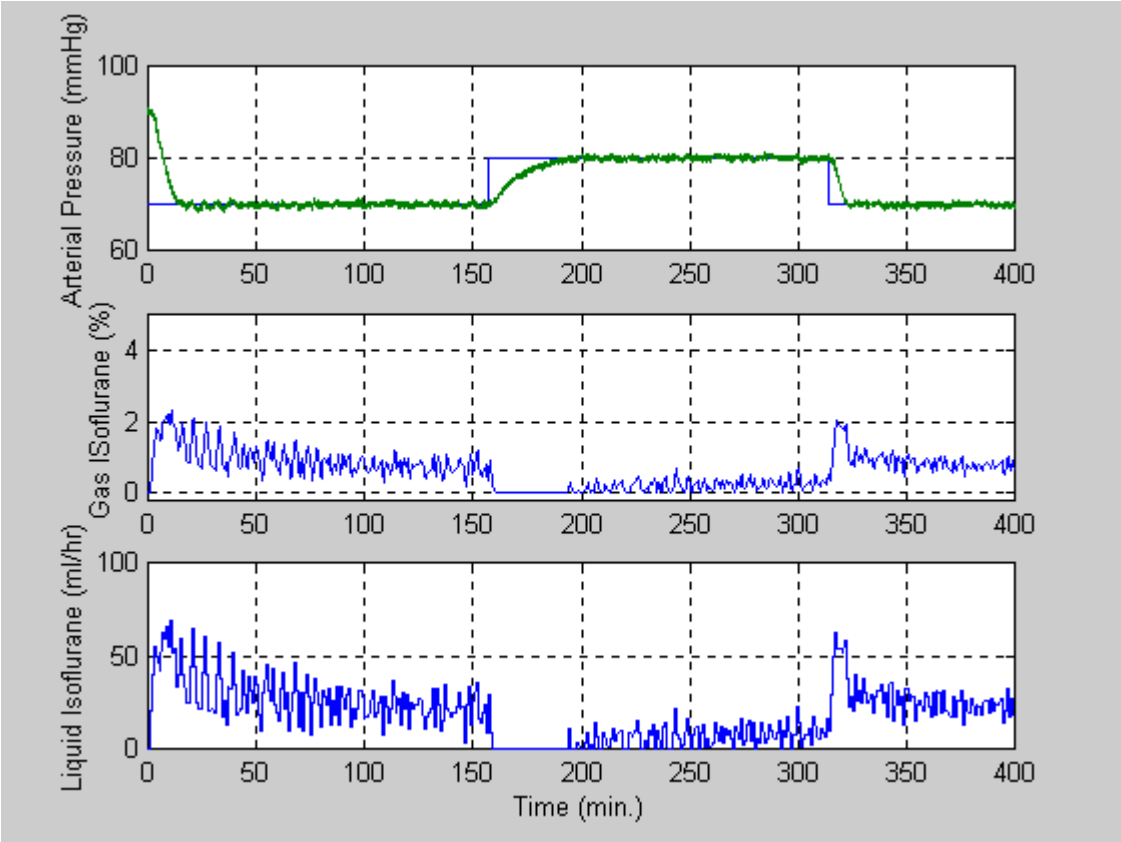

Figure 5. Fuzzy constrained GPC using the simulated anaesthesia model.

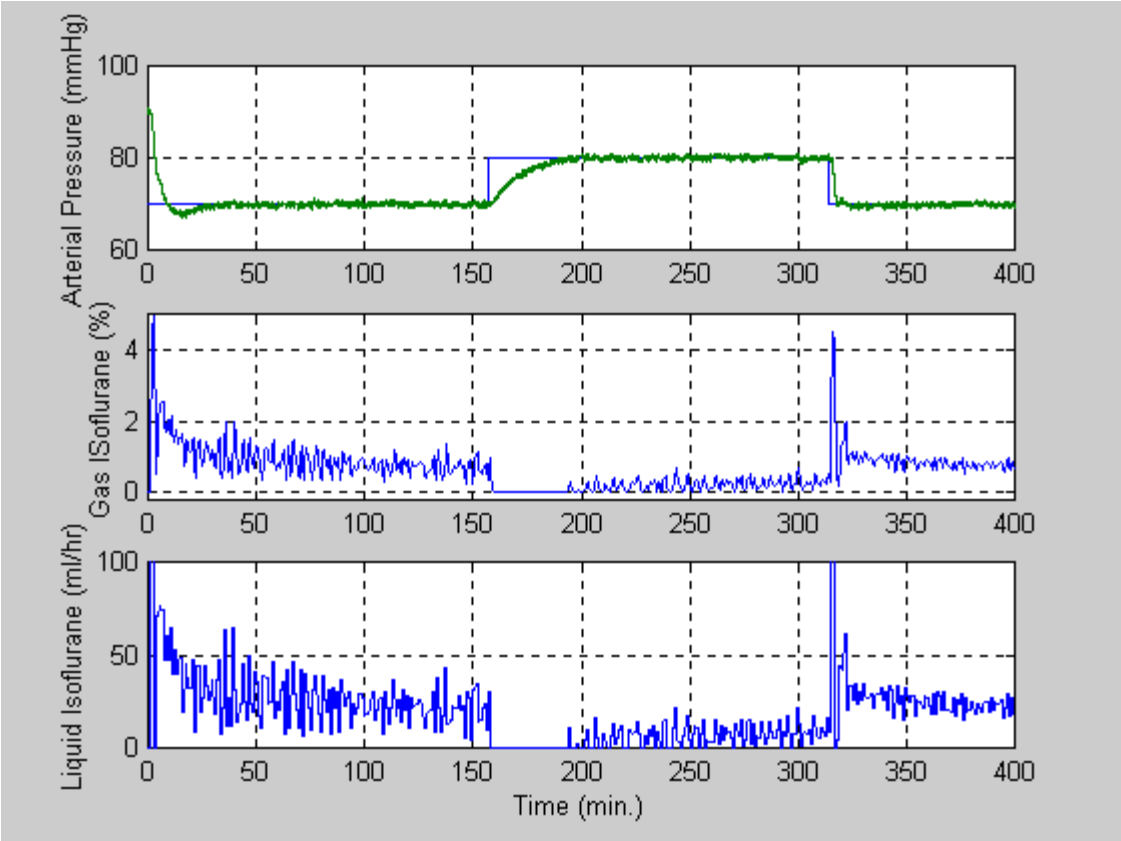

Figure 6. Fuzzy unconstrained GPC using the simulated anaesthesia model.

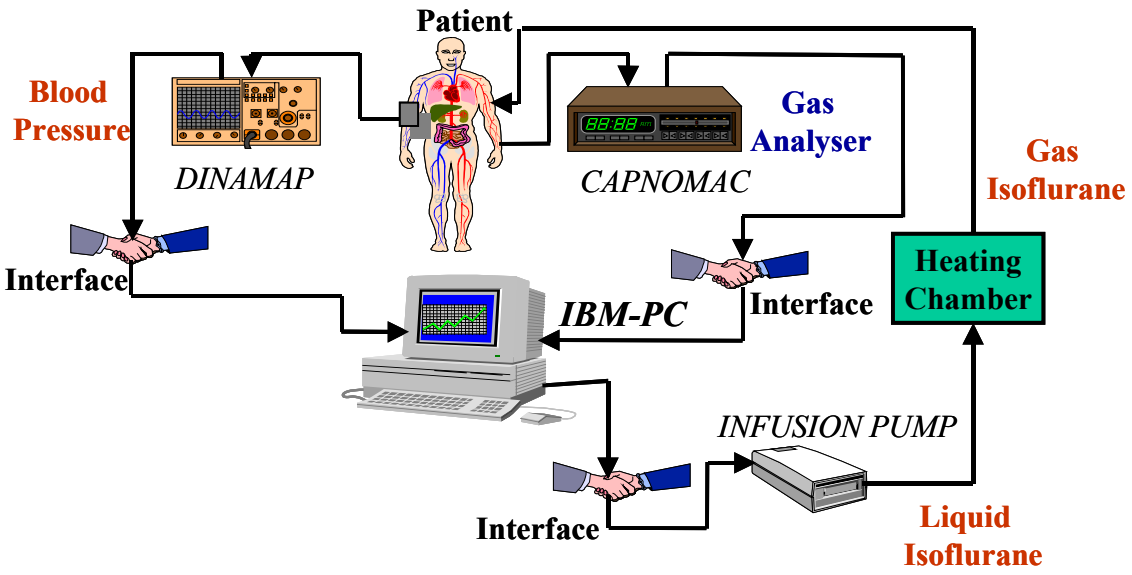

Figure 7. Diagram representing the closed-loop control system as used in the operating theatre to monitor anaesthesia via blood pressure measurements.