ADAPTIVE CONTROL OF LOW-FLOW ANAESTHESIA USING A MIXTURE OF ANAESTHETIC GASES

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Abstract: This paper investigates the automatic control of low-flow inhalational anaesthesia using a mixture of isoflurane and nitruous oxide gases. An adaptive constrained multivariable GPC method is used to compute the isoflurane infusion rate and the nitrous oxide concentration in the fresh gas based on measurements of the end-tidal isoflurane concentration and mean arterial prex`ssure (MAP). In the second part of the paper, the same strategy is employed to control the end-tidal isoflurane concentration using the fresh-gas flow rate and the isoflurane infusion rate as manipulated variables. The feasibility of the proposed control strategies is evaluated on an extended nonlinear compartmental model of the anaesthesia system, which include the pharmacokinetic and pharmacodynamic equations associated with the second anaesthetic gas. Numerical simulations are used to demonstrate the approach.

Keywords: Predictive control, adaptive control, parameter estimation, disturbance rejection, model-based control

1. INTRODUCTION

In most operating theatres, it is common practice to deliver the volatile anaesthetic using a combination of oxygen and nitrous oxide as the carrier gas. Nitrous oxide has good analgesic effects, but cannot be used on its own as an anaesthetic gas. The main role of nitrous oxide in anaesthesia is to potentate the effects of the principal anaesthetic gas.

Administration of high concentrations of N_2O, which is a rapidly absorbed gas, facilitates the rate of rise in alveolar concentration of a simultaneously administered second gas.

Nitrous oxide (the first gas) is taken up from the alveoli in large quantities and is replaced by the inspired gas, thus, effectively increasing alveolar concentration. This increases the supply of the main anaesthetic gas, isoflurane in this case, in the alveoli. The alveolar concentration is thereby increased leading to a more rapid rise of isoflurane concentration in the body. This phenomenon is known as the second gas effect. It is immediately apparent that an advantage of using N_2O is that, assuming a constant flow rate, it effectively reduces patient response times compared to the case when oxygen only is used as a fresh gas.

This article investigates the the automatic control of low-flow anaesthesia using a mixture of isoflurane and nitruous oxide gases. An adaptive constrained multivariable GPC method (Clarke, 1988) is proposed to compute the isoflurane infusion rate and the nitrous oxide concentration in the fresh gas based on measurements of the end-tidal isoflurane concentration and mean arterial pressure (MAP).

During a typical surgical intervention that requires complete anaesthesia, the flow rate of the fresh gas flow rate is adjusted by the anaesthetist several times. In order to further reduce the variables that need to be adjusted manually, the second part of this article investigates the feasibility of adjusting automatically the fresh-gas flow rate as well as of the isoflurane infusion rate to regulate the end-tidal isoflurane concentration and MAP during low-flow anaesthesia.

As in a previous study, accurate tracking has only been enforced for the end-tidal isoflurane

concentration. MAP disturbances caused by surgical stimulation and/or blood loss are dealt with by switching the control error weighting matrix R to enforce set-point tracking of MAP.

3. MODELLING THE SECOND GAS EFFECT

The simulation studies involving a mixture of anaesthetic gases are based on an extended nonlinear compartmental model of the inhalational anaesthesia system. The anaesthesia system and the model have been detailed in a companion paper (Coca, *et al.*, 2005). The single gas model used there has been augmented with the pharmacokinetic equations that describe the evolution of nitrous oxide concentration in the 12 body compartments. The pharmacodynamic equations have also been modified to account for the additional effect of N_2O concentration

$$g_i = g_{i,0}(1 + b_i p_i + b_{i,N_2O} p_{i,N_2O}) \quad (1)$$

$$CO = CO_0(1 + a_1 p_1 + a_2 p_2 + a_A p_A + a_4 p_{1,N_2O} + a_5 p_{2,N_2O} + a_6 p_{A,N_2O}) \quad (2)$$

where p_i and p_{i,N_2O} represent the concentration of isoflurane and nitrous oxide in the compartments i=1-9, p_A and $p_{A,\ N_2O}$ represent the concentration of isoflurane and nitrous oxide in the arterial blood, g_i represent conductivities that are used to calculate the flow in each compartment and CO is the cardiac output, which is calculated as a function of the anaesthesia-free cardiac output CO_0 and concentration of anaesthetic gases in three compartments brain, myocardial and arterial.

When using multiple anaesthesia gas mixtures (especially N_2O) the transport of anaesthesia from the lung to the blood is influenced by concentration changes of gases that are used in high concentrations (Zbinden, 1991).

The increased rate of uptake of isoflurane because of the presence of a second agent, the so called second gas effect, was modelled as in (Frei, 2000) by artificially increasing the alveolar ventilation $Q_{AV}=f_R(V_A-V_{AD})$ in the differential equation of the lung compartment by the factor K_{FF} that depends on the gas concentration mixture in the lung and in the veins:

$$Q_{AV} = Q_{AV\,0}(1 + K_{FF}(p_{insp}, p_{insp,N_2O}, p_{V,N_2O})) \quad (3)$$

For the usual operating point with p_{insp,N_2O} =70[vol%] and $p_{insp,O}$=30[vol%] the factor K_{FF} was set to K_{FF} (70)=0.235 chosen from experimental data (Nicolet, 1995) and was set independent from p_{V,N_2O} . For values below 70%, K_{FF} was assumed to vary linearly with respect to the concentration of nitrous oxide p_{insp,N_2O} such that $K_{FF}(0)=0$.

More details of the multiple gas model can be found in (Deringhetti, 1999; Frei, 2000).

4. THE ADAPTIVE CONTROL STRATEGY

The adaptive GPC algorithm was used to compute the isoflurane infusion rate and the nitrous oxide concentration in the fresh gas based on measurements of end-tidal isoflurane concentration and the mean arterial pressure. In the second simulation scenario, the nitrous oxide concentration is kept constant and the fresh gas flow rate and isoflurane infusion rate are adjusted automatically. The overall control objective is to achieve accurate set point tracking for the end-tidal concentration and keep the mean arterial pressure within a ±5% band relative to the specified set point. The system is supposed to follow closely the end-tidal set point reference under normal operating conditions but to react to significant MAP disturbances due to surgical stimulation for example.

In simulations, the full (26-dimensional) nonlinear model was used in place of the anaesthesia delivery system and the patient. The adaptive multivariable GPC algorithm was implemented using an approximate linear discrete-time model of the process

$$y(t)=(\mathbf{I}-\mathbf{A}(z^{-1}))y(t)+\mathbf{B}(z^{-1})u(t-1), \quad (2)$$

where $\mathbf{A}(z^{-1})$, $\mathbf{B}(z^{-1})$ are polynomial matrices of appropriate dimensions, $y(t)=[y_{MAP}(t)\ \ y_{Endt}(t)]$ represent the MAP and the end-tidal anaesthetic concentration respectively and $u(t)=[u_{isf}(t)\ \ u_{N_2O}(t)]$ represent the anaesthetic infusion rate and the concentration of N_2O in the fresh gas.

The discrete model that was used to implement the GPC algorithm was initially derived off-line, based on simulated input/output data, using system identification techniques. The structure of the model (maximum input lag n_b=6, maximum output lag n_a=4 and the delay n_k=0) were determined following an iterative search. The coefficient matrices corresponding to $\mathbf{A}(z^{-1})$ and $\mathbf{B}(z^{-1})$ were subsequently re-estimated on-line during the simulation.

The set of future control signals were calculated using a multivariable GPC algorithm by optimising the usual finite horizon multivariable (R, Q weighted) quadratic criterion:

$$J(N_1,N_2,N_u)=\sum_{j=N_1}^{N_2}\left\|\hat{y}(t+j)-\omega(t+j)\right\|_R^2+\sum_{j=1}^{N_u}\left\|\Delta u(t+j-1)\right\|_Q^2 \quad (3)$$

subject to absolute constrains of the manipulated variables (u_{isf}, u_{N_2O}, u_{ff}), end-tidal isoflurane concentration (y_{Endt}) and MAP (y_{MAP}).

$$\begin{cases} 0 \le u_{isf}(t) \le 1.5 \\ 0 \le u_{N_2O}(t) \le 70 \\ 1 \le u_{ff}(t) \le 10 \\ 0.4 \le y_{Endt}(t) \le 1.5 \\ y_{MAP}(t) \ge 65 \end{cases} \quad (4)$$

In equation (3) $\hat{y}(t+j)$ is the j-step ahead prediction of the system output, ω is the reference trajectory or future set points for the output, R and Q are positive definite weighting matrices.

In the simulation studies presented in this paper, the constrained linear least squares problem specified by equations (3) and (4) was solved using a two-step quadratic programming algorithm similar to that proposed in (Gill, *et al.,* 1984).

The control of the end-tidal isoflurane concentration was evaluated by comparing the step changes of the target end-tidal concentration using the following performance criteria:

a) Response time – time to reach the target value for increasing and decreasing step changes (from 10% to 90% of the step height).

b) Maximal overshoot – maximum amount that the system overshoots or undershoots the target value after the target value has been reached for the first time.

c) Control effort – quantity of liquid anaesthetic used

5. SIMULATION RESULTS – CASE 1

In this section, numerical simulations are used to demonstrate controller performance in set-point tracking of end-tidal isoflurane concentration and disturbance rejection of MAP. The manipulated variables are the isoflurane infusion rate and N_2O concentration in the fresh gas. Figure 1 shows control behaviour in low-flow conditions, FF=1 l/min, for the following choice of controller parameters: $N_1 = 1$, $N_2 = 10$, $N_u = 5$. The model parameters were estimated on-line using a recursive least squares algorithm with an initial value of the covariance matrix $\Phi=10^3 I$ (where I is the identity matrix) and the forgetting factor ρ=0.97. In this case, R and Q are diagonal matrices of dimension $2N_2$ and $2N_u$ respectively. The first N_2 elements of R (corresponding to y_{MAP}) are equal to r_{MAP}=0.001 and the remaining N_2 elements (corresponding to y_{Endt}) are equal r_{Endt}=1 The control weightings are taken as $q_{u_{isf}}$=1, $q_{u_{N_2O}}$=0.001.

The response times for increasing/decreasing step changes of 0.4% were T_{up} =25s, T_{down}=216s. The corresponding overshoots σ_{up}=8%, σ_{down}=2%. Total amount of anaesthetic used was V_{isf}=11.2ml. The maximum concentration of nitrous oxide in oxygen (input constraint) was set for the controller at 70%. The total amount of nitrous oxide used was V_{N_2O}=6.49 l. The response time at decreased step changes was about half of the response time determined in the case analysed in a companion paper (Coca, *et al.*, 2005), in which nitrous oxide was not used.

It is interesting to compare the simulation results with real clinical evaluations of low-flow anaesthesia control systems that involve mixtures of carrier gases. A clinical study (Sieber et al., 2000) has investigated the use of an automatic feedback control system to adjust the end-tidal concentration using a low-flow approach. The clinical studies were conducted using a nitrous oxide concentration in oxygen of 70%. The flow rate was set to a value of 6 l/min initially then reduced to 1 l/min ten minutes later. The automatic controller was evaluated over a two hour interval. Assuming the concentration of N_2O was kept constant (as it can be inferred from the article), a conservative estimate of the amount of N_2O used would therefore be V_{N_2O} =119 litres.

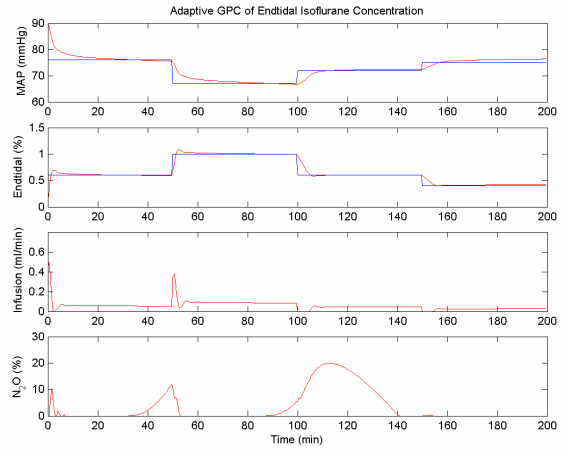

Fig. 1. Simulation study at low flow rate FF=1 l/min.

The reported time responses to decreasing/increasing step changes of 0.3%(volume) were T_{down}=248s, T_{up}=116s. The values are in line with the values that were obtained in simulations described here. The simulation results however suggest that a far smaller amount of nitrous oxide could be used to achieve similar or better controller performance.

5.1 Disturbance rejection

The R matrix is used to weight the output deviations in order to compensate for different output ranges and also to achieve more vigorous closed loop behaviour. In this particular case, R is used to prioritise between the two control performance objectives: set-point tracking of MAP and the end-tidal concentration. In this simulation, accurate set-point tracking of the end-tidal anaesthetic concentration represents the main control objective and it is used as a main indication of the depth of anaesthesia.

The MAP controller is mainly used for disturbance rejection as reference point tracking is not a priority. In practice, when the end-tidal concentration is used as the main indicator of the depth of anaesthesia, the

main performance goal for MAP control would be to maintain the blood pressure value in a band of ±5mmHg (Derighetti, 1999).

The control behaviour when the MAP disturbance of +10 mmHg is applied at t=60 for 15 minutes is illustrated in figure 2. The weight matrix R was switched over the disturbance period such as r_{MAP}=1, r_{Endt}=0.01. The total amount of anaesthetic used was V_{isf}=12.4 ml. The total amount of nitrous oxide used was V_{N_2O} = 42.26 l. As expected, the main effect of using a mixture of nitrous oxide and oxygen as the carrier gas flow is to reduce significantly the response times compared to the oxygen only case.

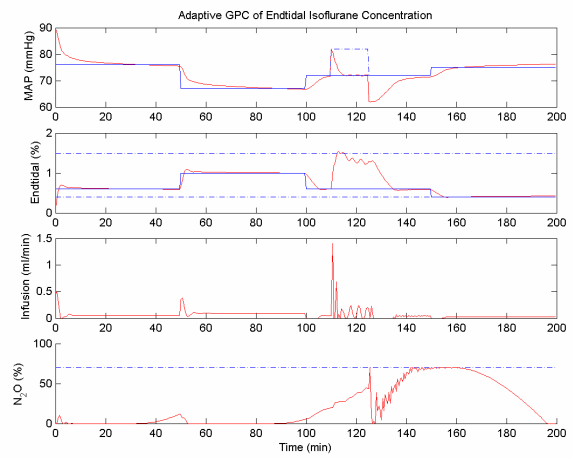

Fig. 2. Disturbance rejection at low flow rate FF=1 l/min.

The MAP response time in this case was T_{down}^{MAP} =160s. This is less than half of the response time obtained for the single anaesthetic gas simulation at high flow rates FF=10 l/min (Coca, *et al.*, 2005).

The only constraint violation was observed for MAP which dropped briefly below 65mmHg after the disturbance was removed. However, both end-tidal isoflurane concentration and nitrous oxide concentrations were kept between the prescribed intervals. This is extremely important since high concentrations of anaesthetic gases can lead to hypnotic crisis or even cardiac arrest (Gentilini, *et al.,* 2001).

The simulations in this section suggest that setting N_2O concentration automatically is feasible and could reduce consumption of N_2O in operating theatres. Nitrous oxide is classified as a greenhouse gas, so reducing consumptions (and hence unwanted emissions) of this gas is desirable.

6. SIMULATION RESULTS – CASE 2

Numerical simulations are used to evaluate the performance of the end-tidal adaptive predictive controller in the case when the manipulated variables are the isoflurane infusion rate and the fresh gas flow rate.

Similar to the previous study, the adaptive multivariable GPC algorithm was implemented using an approximate linear discrete-time model of the process which was identified off-line. The estimated coefficients were used to start the GPC algorithm. Subsequently, the coefficients were re-estimated on-line during simulation. All the simulations in this section assumed a nitrous oxide concentration in the fresh gas flow of 50%.

Figure 3 shows the simulation results for the following choice of controller parameters: $N_1 = 1$, N_2=10, $N_u = 5$, r_{MAP}=0.001, r_{Endt}=1, $q_{u_{isf}}$=0.1, q_{ff}=0.01. The response times for the ±0.4% step changes were T_{down} =99s, T_{up} =27s. The overshoots associated with these step changes were σ_{up}=10%, σ_{down}=3%. The total amount of anaesthetic used was V_{isf}=16.2ml.

The controller behaviour shows that under normal operating conditions, without disturbance, there was an increase of the fresh gas flow rate following decreasing step changes. This has the effect of increasing the washout of anaesthetic from the body. Compared with the simulation carried out at constant fresh gas flow the anaesthetic consumption is slightly higher but the response times were half those at constant gas flow (1l/min).

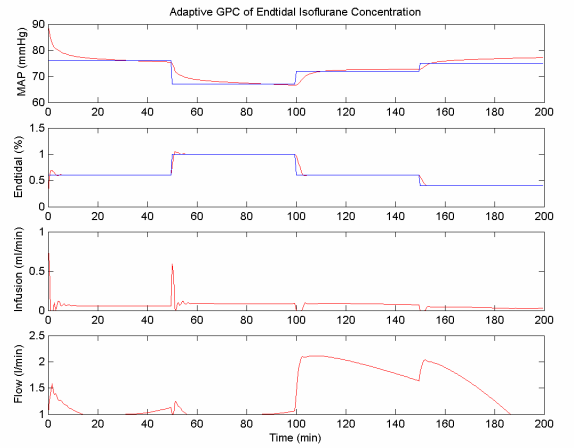

Fig. 3. Adaptive GPC of end-tidal isoflurane concentration using isoflurane and fresh gas flow as manipulated variables.

6.1 Disturbance rejection

A disturbance of +10 mmHg was applied at t=110 min. At this point, switching the weight matrix R, r_{MAP}=1, r_{Endt}=0.01, ensured that controlling MAP has higher priority.

Figure 4 shows that the controller responded fast by increasing the anaesthetic infusion rate. The MAP response time was T_{down}^{MAP} =360s. The fresh gas flow rate in this case has less influence as the response times for increasing end-tidal step changes are less dependent of the fresh gas flow rate (Coca, *et al.*, 2005). The total amount of anaesthetic used was V_{isf} =16.98 ml.

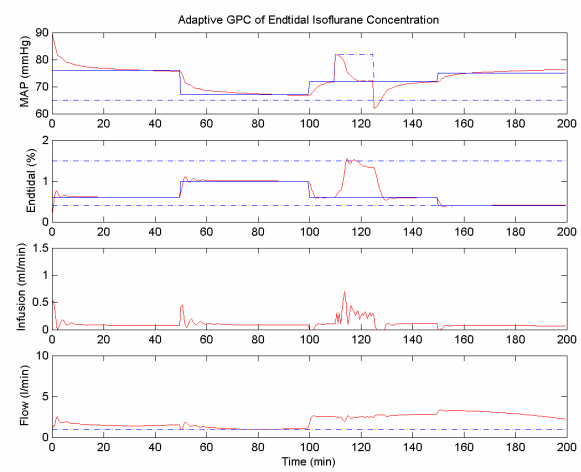

Fig. 4. Disturbance rejection behaviour.

For the same controller response time to the MAP disturbance, in this case the volume of anaesthetic used was less than one fifth of the amount determined from a simulation involving a fixed flow rate of 10 l/m.

7. CONCLUSIONS

An adaptive constrained GPC algorithm was used to regulate low-flow anaesthesia involving a mixture of anaesthetic gases. In a first study, the GPC algorithm was used to set the anaesthetic infusion rate and concentration of nitrous oxide in the fresh gas based on the end-tidal and MAP target signals. In the second study the same control strategy was used to set the anaesthetic infusion rate and fresh gas flow rate based on the same target signals.

In the first simulation case the response times for increasing step changes of end-tidal concentration at low-flow rates were comparable to those achieved at high flow rates where nitrous oxide was not used. In particular, disturbance rejection was very effective owing to the second gas effect. At the same time, this study has indicated that the automatic delivery of nitrous oxide would significantly reduce consumption of this greenhouse gas leading to important cost savings and reduced atmospheric emissions.

The second simulation scenario has shown that by using the fresh gas flow as an additional manipulated variable, it is possible to achieve response times comparable to high flow rates while keeping anaesthetic consumption at levels associated with low-flow anaesthesia. Again the implications are both economical as well as environmental (Cotter, *el al.*, 1991; Langbein, *et al.*, 1999).

It is important to note that the results of the simulations, response times and anaesthetic consumption in particular, are well in line with automatic (using different control techniques) and manual clinical low-flow anaesthesia studies reported in the literature (Zbinden et al., 2000), (Cotter et al., 1991). This emphasises the validity of the mathematical models used and the relevance and importance of such simulation studies in the development of robust, effective and safe automatic anaesthesia control systems.

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