AN ADAPTIVE GPC APPROACH TO LOW-FLOW ANAESTHESIA

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Abstract: An adaptive method is developed to control the end-tidal isoflurane concentration using a low-flow method. The isoflurane concentration is calculated based on measurements of the end-tidal isoflurane concentration and mean arterial pressure (MAP) using a model-based multivariable GPC algorithm. The control design allows explicit handling of input and output constrains, accommodates model uncertainty and takes into account possible MAP disturbances caused by surgical stimulation and blood loss. The proposed approach was tested on a complex nonlinear compartmental model of the anaesthesia system. The simulations demonstrate that the proposed control approach provides fast response, accurate set-point tracking and has good disturbance rejection behaviour. The advantages and drawbacks of low-flow over high flow anaesthesia techniques were evaluated using control-related performance criteria.

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

1. INTRODUCTION

During conventional inhalational anaesthesia a considerable amount of anaesthetics is exhaled practically unchanged in the expired air of anaesthetized patients because the fresh gas flows exceed patient gas requirements by a large margin.

In order to enable reuse of the expired anaesthetic, low-flow anaesthesia uses a low fresh gas flow rate, which can be oxygen or a mix of nitrous oxide and oxygen. According to some authors (Baum, 1995; White, 1992), a low-flow anaesthesia system is one which uses fresh gas flow rates that allow a given level of re-breathing (re-breathing fraction of 50%). A more practical definition has been suggested by (Meakin, 1999), which specifies that in low-flow anaesthesia the fresh gas flow rate should be less than the patient alveolar ventilation. Low-flow anaesthesia is considered to be an efficient way of reducing the consumption of volatile anaesthetic agents. The new volatile anaesthetics such as isoflurane, enflurane and sevoflurane that are used in inhalational anaesthesia are expensive. For economic reasons (Cotter et al., 1991; Baker, 1994), environmental concerns (Langbein et al., 1999) and because of potential health risks to personnel who are constantly exposed to anaesthetic gases there has been a growing interest in low-flow anaesthesia techniques despite the fact that it requires more expertise.

In low-flow anaesthesia differences between machine settings and inspired concentrations can be significant. Changes in the fresh gas concentration have a delayed effect on the end-tidal (expired gas) concentration, which makes it difficult to predict the inspired and expired oxygen and anesthetic concentrations. Although the use of anesthetic monitors of end-tidal anesthetic concentrations provide the ability to deliver the correct anesthetic concentrations without regard to the inflow rate, low-flow approaches add to the complexity of manual regulation of anaesthesia and require extra vigilance. In this context, the use of an automated control system could reduce or eliminate the complexity and uncertainty associated with low-flow techniques, facilitating the wider use of this cost-effective method.

In this paper, an adaptive (multivariable) constrained predictive control method (GPC) (Clarke, 1988) will be used to control the end-tidal anaesthesia concentration and to maintain the mean arterial pressure (MAP) within an acceptable

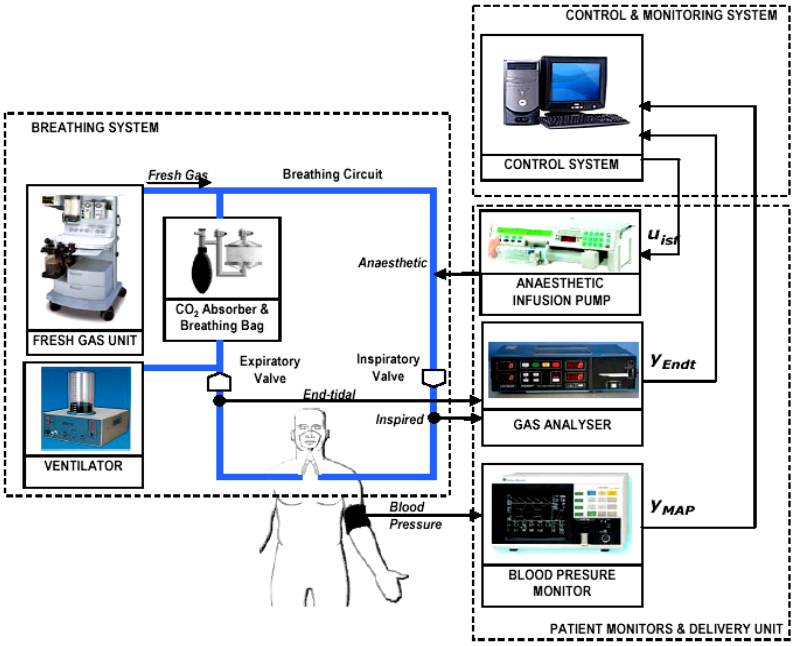

Fig. 1. Anaesthesia control system

physiological range using the infusion rate as the manipulated variable. Because the number of outputs is greater than the number of inputs, accurate tracking will be enforced only for one output variable at a time, while specific constraints are imposed to both input and output variables. In this context the control error weighting matrix R is used as an additional design element to switch between normal and override mode operation. The advantages over earlier approaches developed in (Sieber, *et al*, 2000) and (Vishnoi and Roy, 1991) for example are that the proposed scheme allows for explicit handling of constraints, does not require a state-space model of the process and can compensate for MAP disturbances caused by surgical stimulation and/or blood loss.

2. OVERVIEW OF THE CONTROL SYSTEM

A closed-loop feedback system has been designed to automatically control the depth of anaesthesia by minimising the amount of liquid anaesthetics to be injected into the breathing system. The closed-loop control anaesthesia system presented here uses the inhalational anaesthetic drug isoflurane. According to their functional roles, the system can be decomposed into three main sub-systems:

- the breathing system
- the patient monitors and anaesthetic delivery unit
- the control and monitoring system

A schematic diagram of the system is shown in figure 1. Full details of the hardware and software platform developed for clinical evaluation can be found in (Coca, 2003).

3. MATHEMATICAL MODEL

The simulation studies described in this paper are based on a complex nonlinear compartmental model of the inhalational anaesthesia system. The model includes a model for the anaesthesia delivery system (anaesthetic infusion/vaporisation and respiratory system) and a model describing the uptake, distribution and effects of the anaesthetic drug isoflurane.

The physiological model part describes the evolution of isoflurane concentration in 12 body compartments and the effects of the anaesthetic gas isoflurane to the patient. A model for the uptake and distribution of an anaesthetic drug was first proposed by (Zwart et al., 1972) where the drug used was halothane. With appropriate modifications of parameters found in published data (Nicolet, 1995; Derighetti, 1999) the model can also be used for other volatile anaesthetics, in this case, isoflurane. The state and measurement equations corresponding to the respiratory circuit are those derived in (Westenkow, *et al.*, 1986; Frei, 2000). Since in the present system a syringe pump was used to deliver the (liquid) anaesthetic rather than a vaporizer, the model was augmented with one additional state equation describing the vaporisation process, the parameters of which have been estimated based on experimental data (Coca, 2003).

The model can be written as a system of nonlinear differential equations

$$\begin{cases} \dot{x}(t) = f(x(t), u(t)) \\ y(t) = h(x(t)) \end{cases}, \qquad (1)$$

where the input of the system is the anaesthetic (liquid) infusion rate $u_{isf}(t)$ and the outputs are the end-tidal (expired) anaesthetic concentration $y_{Endt}(t)$, and the mean arterial pressure (MAP) $y_{MAP}(t)$. The state vector is $x(t)=[p_1 \ldots p_9\ p_L\ p_A\ p_V\ p_{vap}\ p_R]^T$ where $p_1, \ldots, p_9, p_L, p_A, p_V, p_{vap}, p_R$ represent partial pressures (concentration) of the anaesthetic in different body

compartments, p_{vap}, is the concentration of anaesthetic vapours in the fresh gas flow, and p_R is the anaesthetic concentration in the breathing circuit. More details of the model are given in the Appendix.

4. THE ADAPTIVE CONTROL STRATEGY

The adaptive GPC method was used to regulate the end-tidal isoflurane concentration and the mean arterial pressure using the infusion rate as the manipulated variable. 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.

For the simulations presented in this paper the full nonlinear model is only used to represent the anaesthesia delivery system and the patient. The adaptive multivariable GPC algorithm was implemented using an approximate linear discrete-time model of the process

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

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 $u(t)=u_{isf}(t)$ is the anaesthetic infusion rate. Although the complete continuous-time model of the patient and the anaesthesia delivery system is 14-dimensional, model reduction techniques applied to a linearised model have shown that the dynamics of the process can be described with good accuracy by a low-dimensional model.

In practice, in order to deal effectively with inter-patient variability, the model has to estimated on-line from measurement data rather than using a theoretical model. The discrete model that was used to implement the GPC algorithm was initially derived off-line using system identification techniques. The structure of the model (maximum input lag n_b=4, 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 $\mathbf{B}(z^{-1})$ are then re-estimated recursively during the simulation.

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

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

subject to absolute constrains of the manipulated variable, end-tidal isoflurane concentration and MAP

$$\begin{aligned} &0\le u_{isf}(t)\le 1.5\\ &0.4\le y_{Endt}(t)\le 1.5\\ &y_{MAP}(t)\ge 65 \end{aligned} \qquad (4)$$

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).

5. SIMULATION STUDIES

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

The performance of the multivariable GPC was evaluated for different tuning parameters and system settings. In particular, the simulations illustrate the dependence of the response time on the weighting matrices R, Q and fresh gas flow rate. Numerical simulations were also used to determine the relationship between fresh gas flow rate and anaesthetic consumption. Figure 2, illustrates typical control performance over a 200 minutes simulation with the following tuning parameters $N_1=1$, N_2=10, $N_u=5$. The model parameters were estimated on-line using the RLS (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 N_u respectively. The first N_2 elements of R (corresponding to y_{MAP}) are equal to r_{MAP}=0.0001 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.

The maximal overshoots corresponding to a 0.4% step increase (t=50*)* and 0.4% step decrease (t=100) of the target end-tidal concentration were σ_{up} =0.8 % and σ_{down}=0.1% respectively. The fresh gas flow rate in this case was FF=10 l/min. At high flow rates the system responds faster to set-point changes. In this case, the response times for decreasing and

increasing step changes (±4%) were T_{up}=21s and T_{down} =39s respectively. The main disadvantage of using high fresh air flow rates is the significant increase in anaesthetic used. The total amount of liquid isoflurane anaesthetic used during this simulation was V_{isf}=97.395ml. Comparatively, the response time at low-flow FF=1 l/min were T_{up}=120s and T_{down} =429s but the volume of anaesthetic used was only V_{isf}=11.565ml. The values determined here

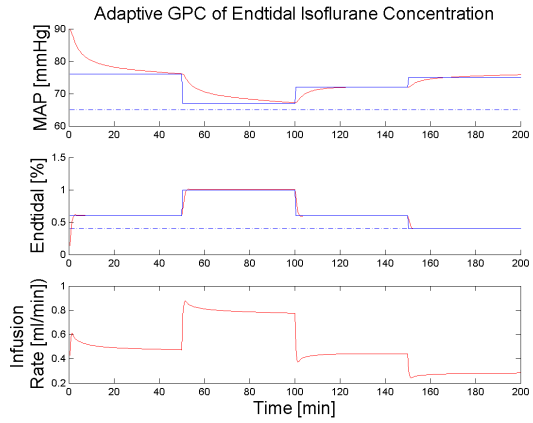

Fig. 2. Simulation study at high flow rate FF=10 l/min.

from simulations are close to the values reported by a clinical evaluation of a model-based control strategy used to regulate end-tidal concentration (Sieber, *et al*., 2000).

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).

A possible approach to reject MAP disturbances, which could be caused by surgical simulations and blood loss, is to switch control priorities once such a disturbance is detected. By implementing this strategy, the controller could compensate effectively for a MAP disturbance (10mmHg) occurring at *t*=110 and lasting 15 minutes, as shown in figure 3. During the disturbance, the additional constrains imposed on the end-tidal output variable prevented the end-tidal concentration to go over the allowed upper limit. In practice, it is very important to prevent overdosing since high concentrations of isoflurane can lead to hypnotic crisis or even cardiac arrest (Gentilini, *et al.,* 2001).

Immediately after the disturbance, no feasible solution could be found to meet all constraints, which meant that MAP was slightly under the specified lower limit for a period of two minutes. The MAP response time in this case was $T_{down}^{MAP} = 370$ s.

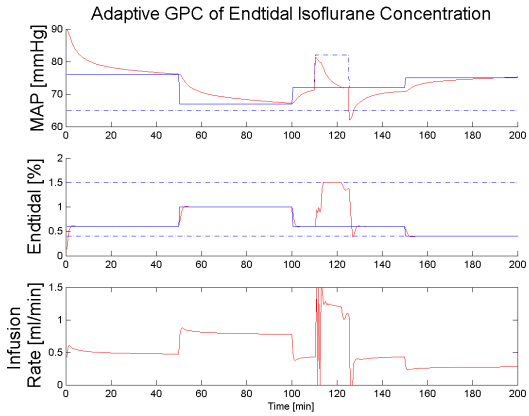

Fig. 3. Disturbance rejection

5.2 Influence of the input weighting matrix Q

The weighting matrix *Q* can be used to smooth the control actions by penalising step changes of the manipulated variable. Larger values of *Q* increase response times. The dependence of the response time on the value of *Q* for a fixed weighting matrix *R* and a fresh gas flow rate FF=10l/min is illustrated in figure 4.

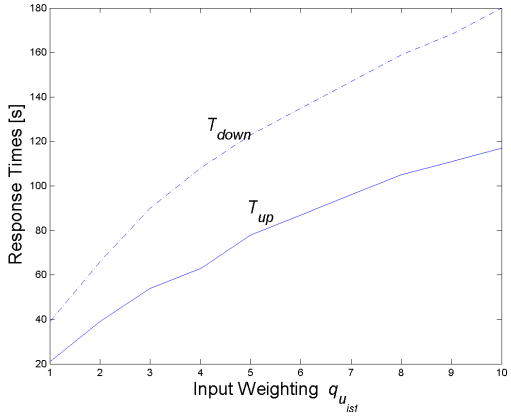

Fig. 4. Dependence of response times of the input weighting matrix *Q*.

5.3 Influence of fresh gas flow rate on the control performance .

The fresh gas flow rate normally varies between 0.5 and 10 l/min. In practice, at high flow rates practically there is no reuse of the anaesthetic gases in the circuit; hence the anaesthetic consumption is higher. At the same time, the system responds faster to step changes in the inspired anaesthetic concentration owing to increased alveolar ventilation, allowing better disturbance rejection. The

dependence of response times on the fresh gas flow rate is illustrated in figure 5. The plot shows a nonlinear dependence of response times on the flow rate. The response times increase faster for decreasing step changes of the targeted end-tidal concentration than for increasing step changes. This is due to the fact that, once the anaesthetic infusion rate is set to zero, how fast the anaesthetic is washed out of the body depends only on the fresh gas flow rate. Above 6 l/min, however, the response times saturate indicating that above this value, the influence of the flow rate on controller performance is negligible. This is the main reason why in practice many anaesthetists use a higher flow rate of at least 6 l/min during the induction (increasing step change) and recovery (decreasing step change) phases.

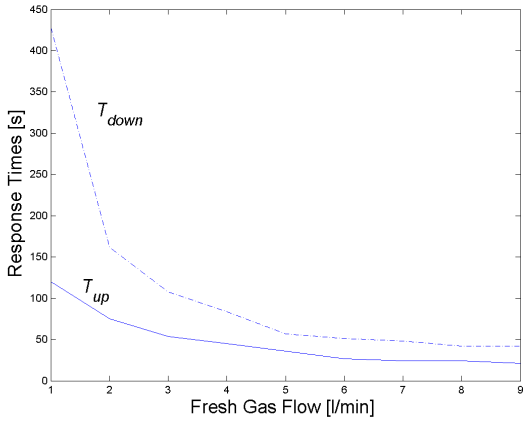

Fig. 5. Response times as a function of fresh gas flow rate

The dependence of anaesthetic consumption on the fresh gas flow rate during controlled anaesthesia, was evaluated for different flow rates (*FF*=1, 2, …, 10) using the theoretical model of the anaesthesia system and identical GPC settings.

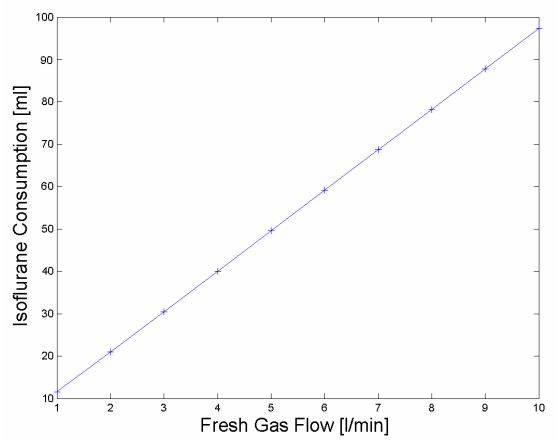

Fig. 6. Dependence of isoflurance consumption on the fresh gas flow.

This dependence is illustrated in figure 6. It shows that consumption of anaesthetic increases linearly with the flow rate and that the amount of anaesthetic used at maximum flow rate (*FF*=10 l/min) is almost ten times the amount of anaesthetic used in low-flow conditions (*FF*=1 l/min).

6. CONCLUSIONS

The performance of an adaptive constrained GPC controller that uses MAP and end-tidal concentration measurements to compute the optimal isoflurane infusion rate subject to input and output constraints was evaluated for different fresh gas (oxygen only) gas flows. This study has revealed that overall, the approach is very effective and that by carefully selecting the two design weighting matrices *R* and *Q*, accurate set-point tracking can be achieved using smooth and efficient control action over the whole range of fresh gas flow rates. In this study, the main objective was to control the end-tidal isoflurane concentration whilst keeping the MAP within ±5mmHg of the target concentration. MAP disturbance rejection was achieved by switching the control error weighting matrix *R* and thus effectively changing control priorities when the disturbance is detected. In these situations, the output constraints placed on the end-tidal concentration prevent overdosing.

The advantages and drawbacks of low-flow over high flow anaesthesia techniques were evaluated using control-related performance criteria. The anaesthetic consumption under automatically controlled delivery was found to vary linearly with the flow rate. The overall consumption at high flow rates (10 l/min) was shown to be almost ten times that at low flow rates (1 l/min), emphasising the effectiveness of low-flow over high-flow techniques.

The main drawback at low-flow rates is the increased response time, in particular for decreasing step changes of the end-tidal concentration. Since usually during decreasing step changes the infusion rate is set to zero, the controller has no influence on the wash-out of anaesthetic, which is determined only by the fresh gas flow rate.

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APPENDIX

The state equation describing the evolution of the partial pressure of isoflurane in nine body compartments is described by

$$p_i(t) = \frac{\lambda_b}{\lambda_b V_{i,b} + \lambda_{i,t} V_{i,t}} q_i(t)[p_A(t) - p_i(t)] \quad (5)$$

where $\lambda_{,b}$, $\lambda_{i,t}$ represent isoflurane solubilities in blood and tissue, $V_{i,b}$, $V_{i,t}$ are the blood and tissue volumes and $q_i(t)$ is the blood flow through the *i*-th compartment. The partial pressure in the lung is given by

$$\dot{p}_L(t) = \frac{1}{\lambda_b V_{L,b} + \lambda_L V_{L,t} + V_{FRC}} \{\lambda_b CO(t)[p_V(t) - p_L(t)] + f_R(V_A - V_{AD})[p_{insp.}(t) - p_V(t)]\} \quad (6)$$

where V_A is the total alveolar space, V_{AD} is alveolar dead space and f_R is the respiratory frequency, V_{FRC} is the functional residual capacity of the lung, $CO(t)$ is the cardiac output and $\lambda_{L,t}$ is the tissue solubility of the lung. The equation for the arterial partial pressure is:

$$\dot{p}_A = \frac{\lambda_b}{\lambda_b V_{A,b} + \lambda_A V_{A,t}} CO(t)[(p_V l_s + p_L(1-l_s) - p_A] \quad (7)$$

where l_s is the lung shunt. The venous partial pressure is described by

$$p_V(t) = \frac{\lambda_b}{\lambda_b V_{V,b} + \lambda_V V_{V,t}} \left[\sum_{i=1}^{9} q_i(t) p_i(t) - CO(t) p_V(t) \right] \quad (8)$$

The cardiac output and blood flow through each compartment are calculated using pharmacodynamic equations

$$CO = CO_0(1 + a_1 p_1 + a_2 p_2 + a_3 p_A) \quad (9)$$

for the cardiac output and

$$g_i = g_{i,0}(1 + b_i p_i) \quad (10)$$

for the conductivities that are used to calculate the flow in each compartment as

$$q_i(t) = CO(t) \frac{g_i(t)}{\sum_{i=1}^{9} g_i(t)} \quad (11)$$

The dynamic equation for the respiratory circuit is given by

$$\dot{p}_R(t) = \frac{FF}{V_R} p_{vap} + \frac{f_R(V_A - V_{AD})}{V_R}[p_L(t) - p_R(t)] - (\frac{FF - Q_\Delta}{V_R}) p_{endt}(t) \quad (12)$$

where Q_Δ is the net uptake of gas, FF is the fresh gas flow rate and p_{endt} is the end-tidal concentration given (Westenkow, et al., 1986) by

$$p_{endt}(t) = \frac{V_{AD}}{V_A} p_{insp}(t) + (1 - \frac{V_{AD}}{V_A}) p_L(t) \quad (13)$$

with $p_{insp}=p_R$. The output equation for MAP is

$$MAP = CO_0 \frac{(1 + a_1 p_1 + a_2 p_2 + a_3 p_A)}{\sum_{j=1}^{9} g_{j,0}(1 + b_j p_j)} \quad (14)$$

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