MULTIVARIABLE FUZZY CONTROL FOR THE SIMULTANEOUS ADMINISTRATION OF THE ANAESTHETIC AND THE ANALGESIC DRUGS

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Abstract

A multivariable fuzzy controller developed for the simultaneous administration of the anaesthetic drug (propofol) and the analgesic drug (remifentanil), is presented. The controller was designed in order to achieve a steady state level of depth of anaesthesia (DOA) and to reduce the amount of drug infused. The multivariable fuzzy controller is based on linguistic rules that interact with three decision tables, one of which represents a fuzzy PI controller. Optimisation using genetic algorithms was used to determine the scaling factors of the fuzzy PI controller. According to the different possibilities for the DOA level and for the surgical stimuli, the multivariable controller defines the required change in the infusion rates of the two drugs. A patient model remifentanil was used to test the multivariable controller. The controller was able to adjust the remifentanil infusion rate according to the stimulus intensity, and takes advantage of the synergistic interaction to the change adequately the propofol infusion rate. The multivariable fuzzy controller was tested under different simulations, and responded efficiently to different induction profiles, set point changes and disturbances.

1 Introduction

"Anaesthesia" and "depth of anaesthesia" are two different entities that are frequently confused because of the sharing of a common word. Anaesthesia can be defines as the lack of response and recall to noxious stimuli. It includes paralysis (muscle relaxation), unconsciousness (depth of anaesthesia) and analgesia (pain relief). Anaesthesia involves the use of three drugs, a muscle relaxant, an anaesthetic and an analgesic. However, the muscle relaxant will not be considered in this research, since it has no influence on the degree of hypnosis, which is the main concern in the operating theatre. The analgesic drug is of more importance since it affects the pharmacodynamics of the anaesthetic. The analgesic and anaesthetic drugs are interconnected, since they interact with each other so as to achieve an adequate level of depth of anaesthesia (DOA) and analgesia.

The anaesthetic and analgesic drugs may have different types of interactions, increasing or decreasing the effects of each drug, potentiating the different side effects or even introducing new side effects [8]. The anaesthetist needs to be aware of the interactions between the drugs for the safety of the patients. These drug interactions provide an insight into the mechanism of general anaesthesia and a practical guideline for the optimal drug dosing during anaesthesia [2,13].

Propofol is the most used intravenous anaesthetic agent and it is usually combined with one of the synthetic opioids so as to provide analgesia. However, the optimal propofol infusion rate and concentration are largely affected by the choice of opioid, and in some cases, by the duration of infusion [16]. An opioid with a rapid onset of action (such as remifentanil) allows for a rapid response to the stimulus effects. Propofol and remifentanil have a synergistic relationship. The effect of the combination of these two drugs is greater than that expected as based on the concentration-effect relationships of the individual agents. The use of remifentanil as the analgesic drug requires more attention than when using other analgesics [14]. Remifentanil is a potent short acting opioid, and the optimal propofol concentration is much lower when combined with remifentanil compared to other analgesics [17]. The unique properties of remifentanil make it a suitable analgesic for use with propofol, and adequate for control in anaesthesia.

A closed-loop control system of DOA will help the anaesthetist in the operating theatre, adjusting the infusion rates of the anaesthetic and analgesic drugs. The majority of the researches in the area are mainly concerned with the automatic control of the anaesthetic drug, whereas the analgesic is controlled manually by the anaesthetist [1,4,9].

However, in this research the objective is a multivariable control structure for simultaneous administration of both drugs (i.e. propofol and remifentanil).

The rest of this paper is organised in five sections. In Section 2, the structure of the proposed closed-loop system and the patient model used in the simulations are presented. The structure of the multivariable fuzzy controller is described in Section 3. The results regarding different simulations are presented in Section 4. Finally, in Section 5 are presented the overall conclusions of the study.

2 Closed-Loop Structure

The closed-loop patient system links a patient model, a DOA classifier and the control algorithms. Figure 1 shows the block diagram comprising of the different components of the closed-loop system during the maintenance phase of anaesthesia. The fuzzy relational classifier for DOA is presented in [10]. This classifier uses a set of features from the auditory evoked potentials (AEP), the change in heart rate (ΔHR) and the change in systolic arterial pressure (ΔSAP) to determine the level of DOA. The DOA is classified according as: 1-Awake; 2-OK/Light; 3-OK; 4-OK/Deep; and 5-Deep. OK is when no patient response is observed under surgical stimulus, i.e. the patient is under the adequate level of DOA.

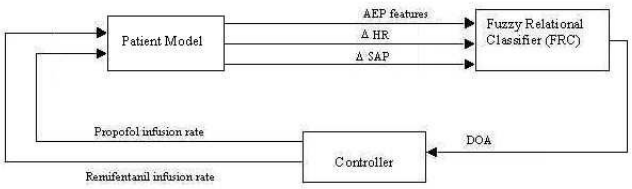

Figure 1. Block diagram of the closed-loop simulation system.

The AEP are the responses in the EEG to clicks applied to the ear. This signal detects the changes that occur in the central nervous system relating to DOA [5,15]. The AEP are processed by averaging and filtering, after which multiresolution wavelet analysis is used to extract a set of features. The AEP and the cardiovascular parameters are used to establish the level of unconsciousness of the patient.

The DOA level in addition to the information about the surgical stimulus (introduced to the system by the anaesthetist), are used to determine the adequate infusion rate of the two drugs. In other words, a multivariable controller maintains and adequate DOA level by adjusting the infusion rates of propofol and remifentanil, which are the inputs to the patient model.

2.1 Patient Model

The patient model used in the simulations is divided into pharmacokinetic and pharmacodynamic models. The compartmental pharmacokinetic models, which use mean population parameters, determine the plasma concentration of both drugs independently. The pharmacodynamic model comprises the effect compartments of the two drugs and a structure of fuzzy models. This fuzzy structure models the wavelet extracted AEP features and the cardiovascular parameters from the effect concentrations and the surgical stimulus, according to the drugs interaction and the effects of the different stimuli intensity. The patient model was developed in [11] using data collected in the operating theatre.

Figure 2 shows the block diagram of the maintenance phase patient model. Only the maintenance phase is modelled because the interaction between propofol and remifentanil is of crucial importance during this phase, due to the continuous presence of stimulus and the properties of the two drugs. Overall, the cardiovascular parameters ΔHR and ΔSAP, and the wavelet extracted AEP features are the result of the drugs concentration, the surgical stimulus and the patient's individual parameters [11,12].

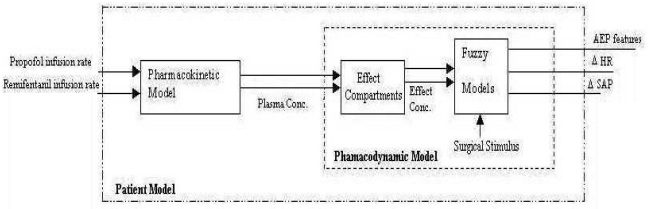

Figure 2. Block diagram of the patient model.

3 Multivariable Fuzzy Controller

Control systems should deliver a minimum amount of the drug, and avoid costly delays from failing to keep the patient in a desired state. A fuzzy controller provides a means of converting a linguistic control strategy based on expert knowledge into and automatic control strategy [6,7].

During general anaesthesia, the anaesthetist is confronted with the dilemma of whether to vary propofol or the opioid (in this case remifentanil). The anaesthetist's knowledge and experience can be incorporated into the fuzzy control system as a set of linguistic rules. In addition, the interaction between propofol and remifentanil introduces information that could be used to determine the adequate combination of the two drugs.

A multivariable fuzzy controller was developed with the anaesthetist coordination. The controller for DOA comprises three different blocks, corresponding to the three possible values of DOA, i.e. the DOA level is the target level (i.e. OK level), or the DOA is lighter than the desired (i.e. OK/Light or Awake level), or the DOA is deeper than the desired (i.e. OK/Deep or Deep level). The controller will act differently according to these three stages.

Considering the three different possibilities for the level of DOA, the structure of the multivariable fuzzy controller is as follows:

- If DOA is OK then *no change*;
- If DOA is light and if:
  - stimulus then *increase remifentanil* (**Remifentanil Rule-Base 1)**;

- no stimulus *then increase propofol* (**Fuzzy PI Controller**);

- If DOA is deep and if:
  - no stimulus and remifentanil high then *decrease remifentanil*;
  - no stimulus and remifentanil normal and propofol high then *decrease propofol*;
  - no stimulus and remifentanil normal and propofol normal then *decrease remifentanil*;
  - stimulus and propofol high then *decrease propofol* (**Fuzzy PI Controller)** and *increase remifentanil* (**Remifentanil Rule-Base 2)**;
  - stimulus and propofol normal then *decrease remifentanil*.

It is important to note that a minimum effect concentration of propofol and remifentanil is required at all times, in order to ensure unconsciousness and prevent arousal. The minimum values were established as 2250 ng/ml and 3.5 ng/ml for propofol and remifentanil, respectively. If the concentrations reach these minimum values, then the infusion rate of propofol will be increased by 0.2 mg/sec and remifentanil will be increased by 0.025 μg/Kg/min.

The multivariable controller is based on linguistic rules that interact with three decision tables, two of which are rule-bases for a change in remifentanil infusion rate (rule-base 1 and rule-base 2) and the other represents a fuzzy PI controller for a change in propofol infusion rate.

3.1 Fuzzy PI Controller

A fuzzy PI controller is designed to control the change in the infusion rate of propofol. The fuzzy PI controller uses the error (target DOA minus measured DOA) and the change of error as inputs. The controller's rule-base is presented in Table 1.

DOA Error	Change of DOA error				
	NB	NS	ZE	PS	PB
NB	NB	NB	NB	NS	ZE
NS	NB	NS	NS	ZE	PS
ZE	NB	NS	ZE	PS	PB
PS	NS	ZE	PS	PS	PB
PB	ZE	PS	PB	PB	PB

Table 1. Rule-base of the fuzzy PI controller for DOA. The inputs are the error and the change of error, and the output is the change in propofol infusion rate. The membership functions are labelled: Negative Big (NB), Negative Small (NS), Zero (ZE), Positive Small (PS) and Positive Big (PB).

The variables are normalised between [-1,1] and the membership functions are Gaussian. The maximum level of change in the infusion rate was set to 4000 mg/hr considering the maximum conditions pre-set by the anaesthetist. The input scaling factors of the controller were optimised using genetic algorithm (GA) with a performance index [3]. The following formula was used for the performance index:

$$PIndex = \lambda_1 \sum_{k=0}^{N-1} k\left|e(k)\right| + \lambda_2 \sum_{k=0}^{N-1} u(k) \qquad (1)$$

where *e(k)* is the error, *u(k)* is the propofol infusion rate and *N* is the number of simulation samples. The weighting parameters λ_1 and λ_2 were chosen to place more emphasis on the error or on the infusion rate, so that an ideal balance between both can be reached. A simple GA was used to minimise the *Pindex*. The GA was implemented using MATLAB for a population of 40 strings each of length 20, with a probability of crossover of 0.95 and a probability of mutation of 0.06. The optimisation was run with the parameters λ_1=0.4 and λ_2=0.6, which were found to be representative of the specifications for the control system, giving a bigger weight to the infusion profile. The patient model was used during the optimisation with a fixed profile of remifentanil as set by the anaesthetist according to a typical surgical procedure. The constant infusion rate of remifentanil results is a steady effect concentration during the maintenance phase, which provides a constant level of analgesia. The GA optimisation led to the value of 0.3754 for the error scaling factor and 7.7713 for the change of error scaling factor.

3.2 Fuzzy Rule-bases for Remifentanil

The remifentanil rule-base 1 and rule-base 2 determine the change in the remifentanil infusion rate according to the stimulus intensity and the change in DOA error. The presence of stimulus is established according to the perceived stimulus intensity (labelled between 0 and 1). A value below 0.25 was considered as no stimulus, because a stimulus intensity below this value has very little, if any, influence in the cardiovascular parameters [11]. Note that the main function of an analgesic is to inhibit the surgical stimulus from reaching the central nervous systems.

The remifentanil rule-base 1 determines the increment in the remifentanil infusion rate when the DOA level is light in the presence of stimulus. The rule-base is shown in Table 2, and uses the stimulus and the change in DOA error as inputs. The change in remifentanil infusion rate is normalised between [0,1], however, the maximum value of the variable was established as 0.03 μg/Kg/min. If the DOA is light, higher changes in remifentanil infusion rate are required in order to respond to stimulus and increase the level of DOA.

Stimulus	Change in DOA error			
	Negative	Zero	Positive Small	Positive Big
Low	Small	Small	Medium	Big
Medium	Small	Medium	Medium	Big
High	Medium	Big	Big	Big

Table 2. Rule-base 1 describing the change in remifentanil infusion rate using the stimulus level and the change in DOA error.

The remifentanil rule-base 2 is used when the DOA is deep, however, there is stimulus present and an increment on the remifentanil infusion rate is necessary. Rule-base 2 is shown in Table 3. The perceived stimulus level and the change in DOA error are used to determine the change in remifentanil infusion rate, similarly to rule-base 1.

The differences between rule-base 1 and rule-base 2, with respect to the membership functions of the change in DOA

error, are due to the pre-defined fact that the DOA level is lighter or deeper than the target level. In rule-base 2, the smaller increment in the infusion rate is predominant, since the DOA is deep and the remifentanil is increased for its analgesic properties. In rule-base 1, the DOA is light, hence, remifentanil is increased as a response to stimulus and for its synergistic properties in order to increase the DOA level.

Stimulus	Change in DOA error			
	Negative Big	Negative Small	Zero	Positive
Low	Small	Small	Small	Small
Medium	Small	Small	Medium	Medium
High	Small	Medium	Medium	Big

Table 3. Rule-base 2 describing the change in remifentanil infusion rate using the stimulus level and the change in DOA error

4 Results and Discussion

The multivariable fuzzy controller was tested under different simulations with the patient model described in Section 2.1. Note that the controller only acts during the maintenance phase of anaesthesia (i.e. after 1500 seconds). The induction phase of anaesthesia, during which the patient is still in the anaesthetic room, is manually controlled by the anaesthetist.

4.1 Simulation 1

In the first simulation, a typical infusion profile of both drugs was used for the induction phase. The DOA level for this simulation is shown in Figure 3. The OK DOA level (target level) is achieved at 1740 seconds. Figure 4 shows the infusion rates of propofol and remifentanil for this simulation.

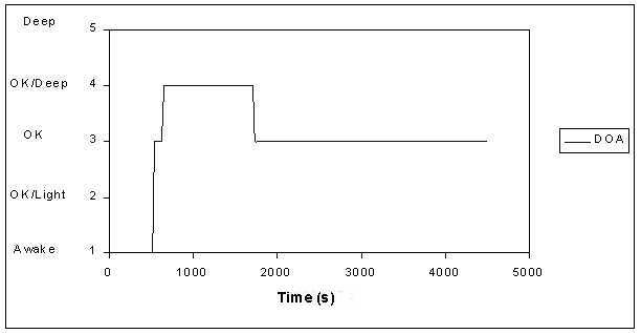

Figure 3. DOA level using the multivariable controller in simulation 1.

The OK DOA level was rapidly achieved, and the controller maintained efficiently a stable DOA level by keeping both infusion rates constant. The multivariable controller reacts to changes in the system output, i.e. the DOA level, when the set point has been reached and the subsequent control action maintained a zero error, then it is not necessary to change the control output.

Next, the same conditions as in simulation 1 were considered, but with a set point change to OK/Deep level at 3000 seconds. Figure 5 shows the infusion rates of propofol and remifentanil as determined by the multivariable controller during the maintenance phase. The DOA level is shown in Figure 6.

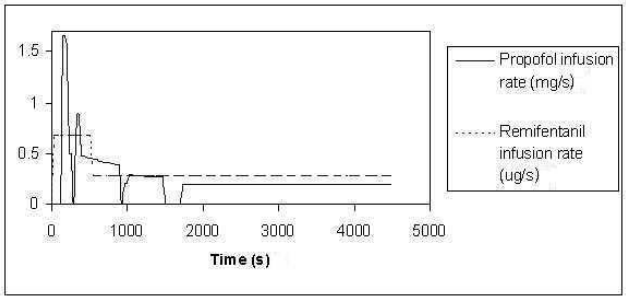

Figure 4. Propofol and remifentanil infusion rates as determined by the controller in simulation 1.

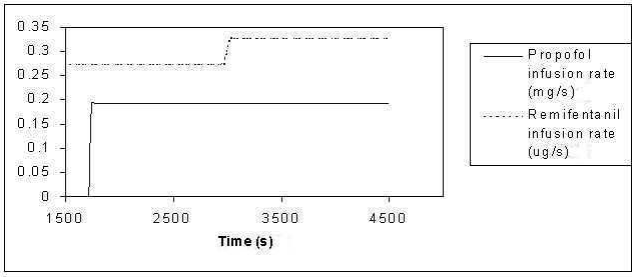

Figure 5. Propofol and remifentanil infusion rates as determined by the controller, during the maintenance phase. DOA target chante to OK/Deep at 3000 seconds.

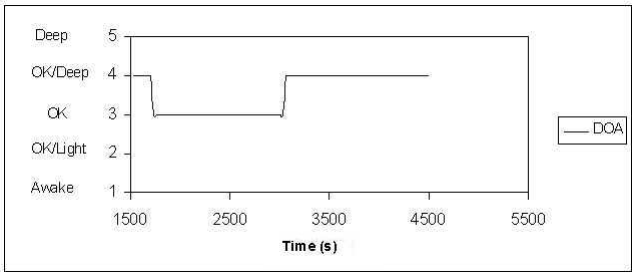

Figure 6. DOA level using the multivariable controller, during the maintenance phase. DOA target change to OK/Deep at 3000 seconds.

The OK/Deep DOA level is reached at 3060 seconds, i.e. only 60 seconds after the set point change. The multivariable controller reacts to the set point change by increasing the remifentanil infusion rate, due to the high stimulus level present in the system at this time. This increase in the remifentanil infusion rate, increases the level of analgesia and also potentiates the effect of propofol. A deeper level of depression is achieved, hence the multivariable controller is taking advantage of the synergism between propofol and remifentanil for an efficient control of DOA.

In order to analyse the response of the controller under different conditions, a set point change to the OK/Deep level at 3720 seconds was considered. Figure 7 shows the propofol and remifentanil infusion rates during this simulation. At 3720 seconds the stimulus intensity is very low, therefore, the controller reacts by increasing the propofol infusion rate.

The DOA level for this simulation is shown in Figure 8. The OK/Deep DOA level is reached at 3870 seconds, i.e. 2.5 minutes after the set point change. The controller is able to achieve the OK/Deep level in both situations in a relatively short time.

In the first case, i.e. an increase of the remifentanil infusion rate, the OK/Deep level is reached faster due to the rapid onset of action of remifentanil, a subsequent reduction in the perceived stimulus, and a synergism with propofol. In the second case, i.e. an increase of the propofol infusion rate, the OK/Deep level is the response to the increase in the propofol effect concentration.

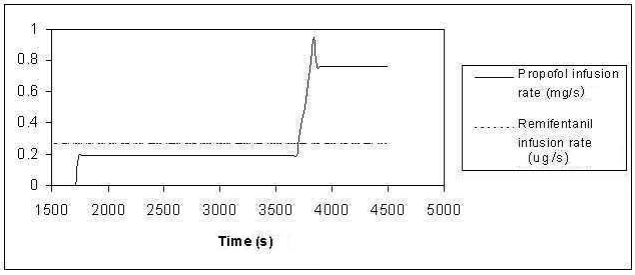

Figure 7. Propofol and remifentanil infusion rates as determined by the controller, during the maintenance phase. DOA target change to OK/Deep at 3720 seconds.

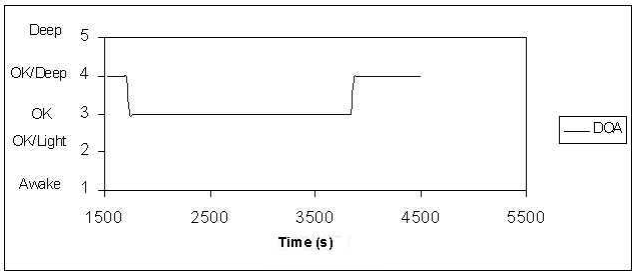

Figure 8. DOA level using the multivariable controller during the maintenance phase. DOA target change to OK/Deep at 3720 seconds.

4.2 Simulation 2

Simulation 2 considers a different propofol infusion profile during the induction phase, hence, different initial conditions for the controller. The remifentanil infusion profile during induction is the same as for simulation 1. The DOA level for this simulation is shown in Figure 9.

At the beginning of the maintenance phase the DOA level is at the OK level (i.e. the target level), hence, the propofol and remifentanil infusion rates are kept constant by the controller. However, at approximately 1900 seconds the DOA level increases to OK/Deep. The multivariable controller responds with a decrease in the remifentanil infusion rate, since the propofol effect concentration is within the normal range. Therefore, there is no change in the propofol infusion rate. Figure 10 shows the decrease in the remifentanil infusion rate. The decrease in the remifentanil infusion rate is very small, but it is proved sufficient in order to achieve the OK DOA level

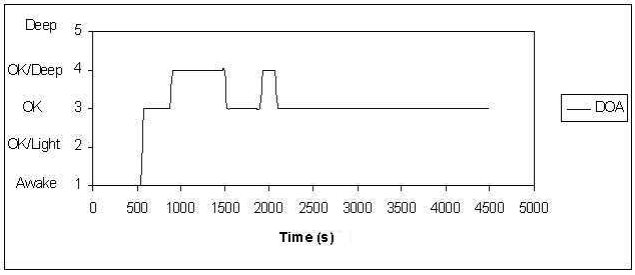

Figure 9. DOA level using the multivariable controller in simulation 2.

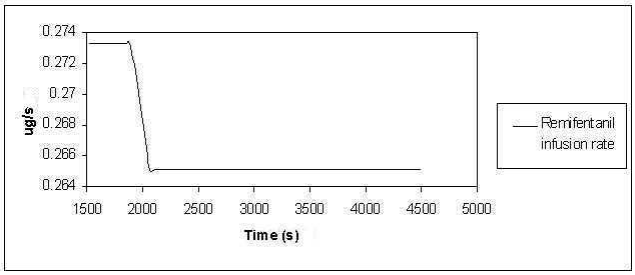

Figure 10. Remifentanil infusion rate as determined by the controller in simulation 2, during the maintenance phase.

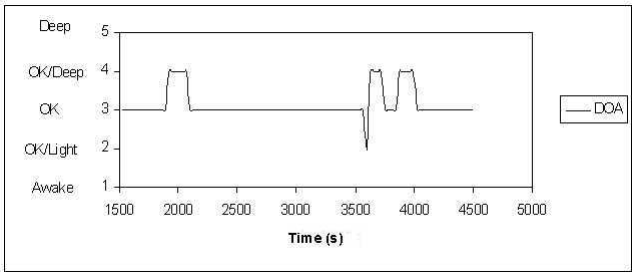

Figure 11. DOA level using the multivariable controller (maintenance phase only). Disturbance to the OK/Light DOA level at 3600 seconds.

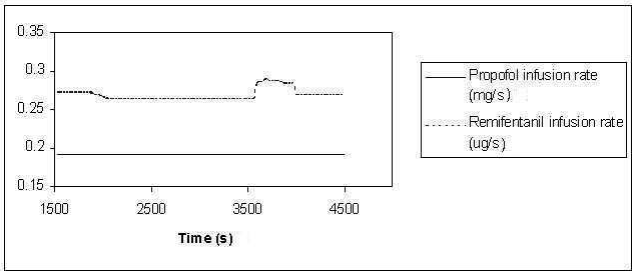

Figure 12. Propofol and remifentanil infusion rates using the controller, during the maintenance phase. Disturbance to the OK/Light DOA level at 3600 seconds.

Considering the same conditions as for simulation 2, a disturbance to the OK/Light DOA level was introduced at 3600 seconds. In a real situation, this could be due for instance to a high stimulus interference. Figure 11 shows the DOA level for this simulation. The first OK/Deep DOA level (at approximately 1900 seconds) is the same as in Figure 9. Figure 12 shows the propofol and remifentanil infusion rates for this simulation. The propofol infusion rate is kept at a constant level from the start of the simulation. The first

decrease in the remifentanil infusion rate is the same as in the simulation 2.

The controller responds to the OK/Light disturbance with an increase in the remifentanil infusion rate, which leads to an OK/Deep DOA level. Therefore, the controller subsequently decreases remifentanil in order to stabilize the effect concentration and lead to an OK DOA level.

5 Conclusions

Fuzzy logic was used to construct a multivariable controller for the simultaneous administration of propofol and remifentanil, which was based on the anaesthetist experience translated to linguistic rules.

In order to test the reactions of the multivariable controller, several closed-loop simulations were performed using different induction profiles, and adding set point changes and disturbances to the system. The controller performed efficiently in all simulations, by adjusting the infusion rate of both drugs in response to DOA changes.

The multivariable controller shows a smooth and gradual reaction to the change in DOA level, which has proved to be efficient in maintaining a stable level of DOA. The fast onset of action of remifentanil allows the controller to manipulate the infusion rate in order to achieve rapidly the desired DOA level. Therefore, the controller is able to respond adequately to the external disturbances. Only small changes in the remifentanil infusion rate were used and proved to be efficient in achieving the OK DOA level.

The infusion rates of both drugs were adequately changed to achieve and maintain a stable DOA level, taking advantage of the interaction between the two drugs. Propofol is titrated to lower infusion rates, decreasing the amount of drug infused, and speeding up recovery. In addition, the controller ensures adequate analgesia by titrating the remifentanil according to stimulus. It was found that it is possible to use information about drug interactions to successfully develop a simultaneous automatic controller of both drugs.

Fuzzy logic techniques proved to be efficient in incorporating human knowledge for a better solution in biomedicine. The complexity of DOA makes it ideal for the application of fuzzy logic based concepts. This system can act as an advisor, to anaesthetists in the operating theatre. The closed-loop system decreases the amount of drug infused, reduces the anaesthetist workload, administers both drugs simultaneously taking advantage of the existent synergism and adjusting to the presence of stimulus, and leads to an overall increase in the patient's comfort and safety.

This is one of the first studies on drug interactions and multivariable control in humans, it can be used as a source of information to rapidly achieve optimal conditions, and would improve the quality of general anaesthesia. In the future, the objective would be the implementation of the system in the operating theatre.

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