AUTOMATIC CONTROL OF ANAESTHETIC DRUG DELIVERY IN A CLOSED-LOOP CONTROL SYSTEM WITH PREDICTION

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ABSTRACT: The automatic titration of the anaesthetic drug propofol in a closed-loop control system to maintain the depth of anaesthesia at a constant adequate level for surgery under general anaesthesia is proposed. Middle-Latency Auditory Evoked Potentials are used as the indicator of choice for obtaining the depth of anaesthesia from the patient using a self-organising neural network. The decision-making system is implemented using fuzzy-logic and the decision is further improved by using a new prediction system.

KEYWORD: Anaesthesia, Middle-Latency Auditory Evoked Response, Fuzzy Control, Prediction.

1. INTRODUCTION

The introduction of balanced anaesthetic techniques involving the use of neuromuscular blocking drugs has made the assessment of depth of anaesthesia (DOA) more difficult because respiratory pattern and spontaneous movement are no longer available as signs of inadequate anaesthesia (Sebel *et al.*, 1985). Through the development in anaesthetic techniques, the danger has moved from too deep anaesthesia and death to that of too-light anaesthesia with the risk of conscious awareness. Assessment of the DOA is now carried out by monitoring the autonomic responses to surgery, but this is not wholly satisfactory as demonstrated by incidence of awareness using balanced techniques. There has as a result been much research carried out on the development of an accurate indicator of anaesthetic depth during surgery. The various signs that have been investigated have all been useful to a certain extent, and the extent of their limitations has varied extensively. Such has been the case that the signs used by the anaesthetist to assess the patient's DOA depend very much on the recipe of drugs used to achieve anaesthesia. The various signs that have been investigated over the years include the isolated forearm technique (Breckenbridge and Aitkenhead, 1981), oesophageal contractility (Guidon-Attali, 1994), the MAC concept (Stanski, 1994) and haemodynamic responses (Kanaya *et al*,. 1994). The latter has become very popular despite their limited use after the introduction of curare which obscured the previously used signs.

Neuromonitoring has recently been acquiring more attention due to the fact that the brain is the site of action of anaesthetic agents. The evoked potentials have been heavily investigated, and among them the middle-latency auditory evoked potentials (MLAEP) has been shown to be the most promising (Thornton 1991). Thornton and Newton (1989) showed that the MLAEP satisfied the four criteria for a signal to be used as a monitor of anaesthetic depth: 1) show graded changes with anaesthetic concentration, 2) show similar changes for different agents, 3) show appropriate changes with surgical events and 4) indicate awareness or very light anaesthesia.

With the recent advances made in the determination of DOA, more and more work has started on the development of the CL control of the latter. Most of them have been carried out in a simulation stage (Shieh, 1994; Webb *et al.*, 1996) and there have also been CL control of DOA carried out on animals (Nayak and Roy, 1998). In 1989, Schwilden *et al.* (1989) used a quantitative analysis of the EEG to control the amount of propofol administered to volunteers; by controlling the median EEG frequency, they were able to abolish response to commands and eyelash reflex was removed. Shieh (1994) used heart rate and systolic arterial pressure to determine the DOA; this was then used to control DOA using propofol and fentanyl (a powerful analgesic) in simulated patients.

2. MIDDLE-LATENCY AUDITORY EVOKED RESPONSE AS AN INDICATOR OF ANAESTHETIC DEPTH

The MLAEPs were recorded (at a sampling rate of 1 KHz) non-invasively in the operating theatre using surface electrodes. The MLAEPs were extracted from the ongoing EEG using ensemble averaging with a relatively low

averaging period of about 30s. Averaging over a larger period might not necessarily produce better quality signals as over large time periods, the signal cannot be assumed to be stationary.

The conventional way of analysing MLAEPs is to select the few characteristic peaks forming the MLAEP (these peaks are labelled Na, Pa and Nb) and then to measure their latencies and amplitudes. It is these values that give an indication of DOA; increasing concentration of anaesthetic under a stable condition would progressively increase the latencies. These values are then used as discriminatory features of the signal. The time domain analysis is only effective if the signal to noise ratio of the signal is good and any residual EEG noise or artefactual peaks will make peak detection difficult and probably give erroneous results. Many researchers have worked in the frequency domain. Schwender *et al.* (1995a) have used the Fourier Transform (FT) of the MLAEPs to determine the DOA. The FT of the signal has limited application as it carries out a frequency analysis over the whole time period of the signal and as such cannot represent the transient nature of the peaks in the signal or select frequency components within a time-frame.

The ability of the Wavelet Transform to deal with non-stationary signals has been demonstrated by numerous publications on the subject (Akay, 1995; Thakor *et al.*, 1993). Not only are they able to represent the different frequency contents in the signal at different time positions but also decompose the signal into its frequency components, thereby allowing an identification of the major oscillatory components making up the MLAEP. Multiresolution Analysis (Daubechies, 1988) was used to decompose the MLAEP into different resolutions allowing a detailed analysis of the behaviour of the signal in its different spectral bands. The decomposed components are analysed for their energy content and these are used as an indication of the DOA. As such, six features representing the energy at different resolutions was extracted (Backory *et al.*, 1998).

After the successful extraction of MLAEPs, the DOA was determined by the use of the Kohonen Self-Organising Map (KSOM) (Kohonen, 1990). The data labelled by the anaesthetist during surgery into one of the four categories OK/Deep (OKD), OK, OK/Light (OKL) and very light/awake (AWAKE) were used to train the network. It was trained using unlabelled data as the KSOM develops a topographic map of the input vectors thereby capturing the topology and probability distribution of the data. The generalisation capabilities were tested on unseen labelled data and this gave a success rate of 71%. When the OK and OKL levels were merged (considered as one DOA, as during general anaesthesia, it is mainly the differentiation from the dangerous AWAKE level that is important), the success rate was 83%. It is difficult to differentiate between the OK and OKL levels as this is often difficult using the signs used by the anaesthetist, and also very often both are often acceptable during general anaesthesia.

It is the successful determination of DOA that is probably the most important part in the development of the CL system as it decides largely the accuracy of the system. The control of the variable (patient) is not feasible if significant changes (DOA) in the variable cannot be accurately measured.

3. PATIENT MODELS

One of the major tasks towards the implementation of a simulated CL control of a system is the description of that system's behaviour in the presence of the relevant disturbances (inputs to the system). In the case of CL control of DOA, the system is the patient, the disturbances are the amount of propofol in the plasma and the surgical stimuli, and the output is the DOA. Propofol induces sedation while surgical stimuli reverse the effects of the anaesthetic drug on the patient thereby reducing the level of sedation.

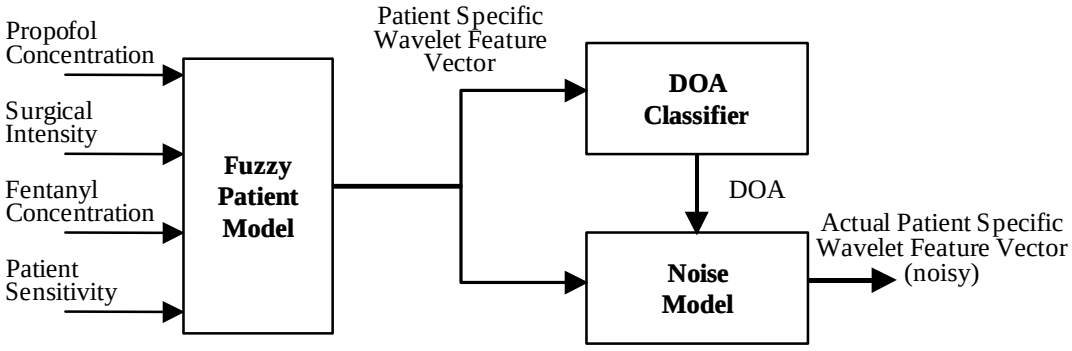

Figure 1 This figure shows the implementation of the patient model.

The massive complexity of biological systems makes it difficult to determine the relationship between the drug dose and the drug effects. In a CL system, the pharmacodynamic patient model is required so that the response of the patient may be predicted based on changes in the relevant input variables; the model has to 'mimic' the response of the actual patient based on the drug dose/concentration and any other variables that may affect the drug's pharmacodynamics. Fuzzy models (Takagi and Sugeno, 1985) can be used to describe processes where the underlying physical mechanisms are not completely known and where the understanding of the process behaviour is mostly qualitative. The use of fuzzy logic as a tool for modelling biological systems has been suggested from as far back as 1969 by Zadeh (1969). It is indeed this high complexity of the human organisms that forces us to accept a level of fuzziness in the description of the behaviour of biological systems.

The expert's (anaesthetist) knowledge was used to develop the knowledge bases of the anaesthetic and analgesic models (Backory and Linkens, 1998). The analgesic model was used to model the level of pain (level of surgical stimulus) induced by surgery under different concentrations of fentanyl. This model was used to determine the perceived level of pain from the actual level of pain (obtained from the anaesthetist after assessing the level of surgical stimulus) and from the concentration of fentanyl obtained from a pharmacokinetic model of fentanyl. The anaesthetic model was the description of the DOA in the presence of a particular concentration of propofol and the level of surgical stimulus, which is a model comparable to the description of DOA as the balance between the depression of the central nervous system by general anaesthesia and its stimulation by surgery. The combination of the two models produce a fairly accurate picture of the actual patient during surgery since the amount of anaesthetic agent required can be dramatically reduced by the use of an analgesic drug. The output of the patient model is a feature vector such as the one obtained after a feature extraction. The patient sensitivity, a value obtained from the amount of propofol required for induction of anaesthesia, was used to scale the patient model output thereby changing the patient model's sensitivity to the drug. Furthermore, random noise obtained from a statistical analysis of actual data was added to the model output to make the model more realistic. The amount of noise added was relative to the DOA since the amount of noise in the MLAEP reduces with increasing DOA. Figure 1 gives a description of the patient model used.

4. CLOSED-LOOP CONTROL DURING GENERAL ANAESTHESIA

A CL system was developed to automatically control an anaesthetic pump for continuous anaesthetic drug infusion to a patient undergoing surgery under general anaesthesia so as to maintain a constant OK DOA using the minimum infusion rate possible. The system comprises: 1) a computer-assisted continuous infusion anaesthetic pump based on a pharmacokinetic patient model (the Target-Controlled Infusion (TCI) system), 2) pharmacodynamic patient models (anaesthetic and analgesic), 3) a classifier to obtain an index for the DOA and 4) a controller to determine the desired plasma concentration of the drug in the plasma.

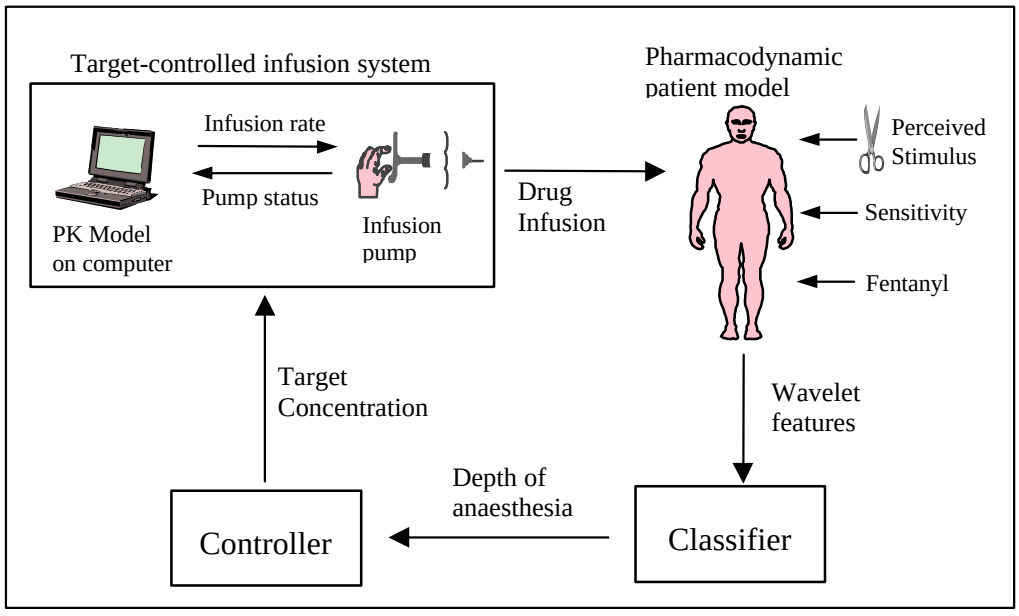

Figure 2 This figure gives an overview of the simulated CL control system.

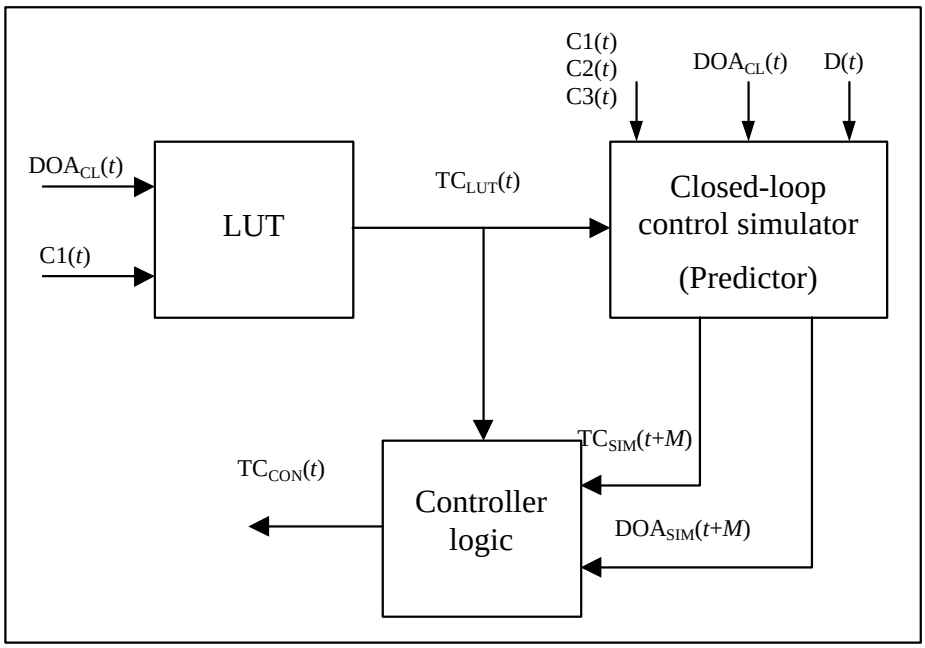

Figure 3 This figure shows the schematic of the controller subsystem incorporating prediction using the predictor.LUT is the lookup-table, C1(*t*), C2(*t*) and C3(*t*) are the concentrations of propofol in the model-based infusion system. $TC_{SIM}(t+M)$ and $DOA_{SIM}(t+M)$ are the target concentration and DOA from the prediction system; they represent the likely values after time *M*.

An overview of the CL system is shown in Figure 2. It indicates how all the components described in the previous section fit together. The controller consisted of a look-up table used as a rule-base which was obtained after consultation with the anaesthetist and the controller logic (a set of if…then rules mimicking the control of anaesthesia by the anaesthetist during general anaesthesia). Among the rules is one which decreases the target concentration of propofol if the DOA has been stable for a preset amount of time.

5. PREDICTION IN THE CLOSED-LOOP SYSTEM

The prediction method is implemented in the controller logic. Figure 3 shows the implementation of the prediction in the controller. The prediction system (predictor) is a copy of the CL system. During its use, it is initialised with the current values representing the variables in the actual CL control system. The predictor is then 'run' for a set prediction time *M* (2 min is used). The output from the predictor then represents the probable DOA of the patient and the target concentration likely to be in use if all variables remain constant.

These two outputs from the predictor are then used in the controller logic so as to achieve a better control of DOA in the patient. For example, the predictor target would be able to indicate the likely effect of a change in DOA. As an example, if DOA goes light and the LUT recommends an increase of 1000 and the predictor target indicates an increase of 2000, then the predictor target would be used as it indicates that an increase of 1000 would not be enough to bring the DOA back to OK. If the predictor was not used, then the target concentration would have had to be increased in smaller successive steps and thereby resulting in a longer response time (time to achieve the desirable DOA).

5. RESULTS

The surgical conditions under which the CL control system were run was derived from an actual surgical procedure. Notes were taken during the surgery which were then used to replicate the surgical procedure by the surgical stimulation levels and the amount and time at which fentanyl was infused. This profile was then fed to the CL control system and the latter was left to automatically infuse propofol to maintain DOA at an adequate level. Figures 4 and 5 show the results obtained for a particular patient. Figure 4 shows the results obtained when the CL control

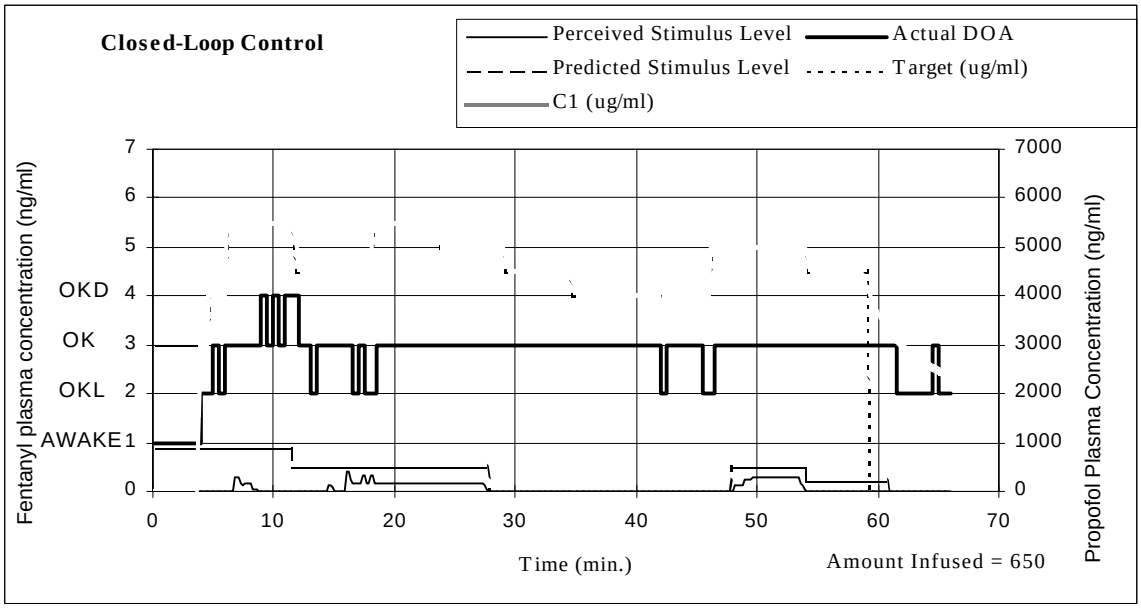

Figure 4 This figure shows the results obtained when the CL control system using the predictor is used to control the DOA of a simulated surgical procedure.

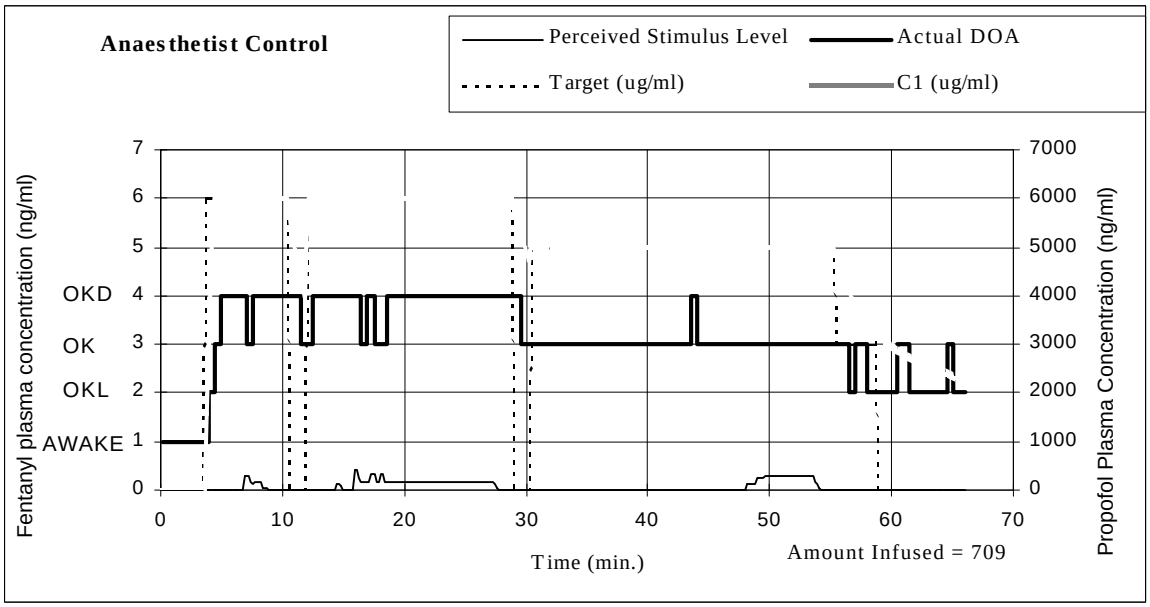

Figure 5 This figure shows the anaesthetic drug profile used during the actual surgical procedure and the DOA achieved.

system automatically infused the anaesthetic drug. Figure 5 shows the actual profile of the anaesthetic drug used and the actual DOA achieved during surgery.

As the results show, the CL control system infused less drug than the anaesthetist and this was reflected by the fact that is achieved a better DOA level than the anaesthetist during the initial 30 minutes. Otherwise, the DOA and TC profiles in both cases are very comparable. About 22 min. into surgery, the CL system also correctly reduced the TC after the DOA had been at an adequate level, and about 43 min. into surgery, the TC was correctly increased when the level of surgical stimulation increased.

5. CONCLUSIONS

The automatic control of anaesthetic drug delivery in a simulated surgical environment has been successfully achieved. The predictor has been successfully integrated in the controller logic to produce a better control of anaesthesia. This predictive knowledge allows the controller to make a 'more informed' decision on the target concentration to be used. Via comparison with the actual anaesthetic drug and DOA profiles achieved by the anaesthetist during the actual surgical procedure, it can be concluded that the automatic control of DOA is achievable.

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