INTELLIGENT SYSTEMS IN BIOMEDICINE

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ABSTRACT: The complexity of biological systems, unlike physical science applications, makes the development of computerised systems for medicine not a straightforward algorithmic solution because of the inherent uncertainty which arises as a natural occurrence in these types of applications. Human minds work from approximate data, extract meaningful information from massive data, and produce crisp solutions. Fuzzy logic provides a suitable basis for the ability to summarise and extract from masses of data impinging upon the human brain those facts that are related to the performance of the task at hand. In practice, a precise model may not exist for biological systems or it may be too difficult to model. In these cases fuzzy logic is considered as an appropriate tool for modelling and control, since our knowledge and experience are directly contained and presented in control strategies without explicit mathematical models. This paper surveys the utilisation of fuzzy logic in medical sciences, with an analysis of its possible future penetration. An application involving fuzzy reasoning and control paradigms in anaesthesia is described in some detail.

KEYWORDS: Fuzzy logic, neuro-fuzzy systems, expert systems, medicine, healthcare, anaesthesia.

1. INTRODUCTION

The complexity of biological systems makes traditional quantitative approaches of analysis inappropriate. There is an unavoidable substantial degree of fuzziness in the description of the behaviour of biological systems as well as their characteristics. The fuzziness in the description of such systems is due to the lack of precise mathematical techniques for dealing with systems comprising a very large number of interacting elements or involving a large number of variables in their decision tree. Fuzzy sets are known for their ability to introduce notions of continuity into deductive thinking. Practically, this means that fuzzy sets allow the use of conventional symbolic systems (specified in the form of tabulated rules) in continuous form. This is essential since medicine is a continuous domain. Many practical applications of fuzzy logic in medicine use its continuous subset feature such as: fuzzy scores, continuous version of conventional scoring systems, and fuzzy alarms. The best developed approach is for fuzzy control, providing the most successful application to date in which a rule-base mapping from input to output variables effectively implements a continuous control law.

In medicine it is not necessary to deal with micro-phenomena and micro-objectives to encounter the problem of incompleteness, uncertainty, and inconsistency. The lack of information, and its imprecise, and sometimes contradictory, nature is much more a fact of life in medicine than in, for example, the physical sciences. These problems have to be taken into account in every medical decision, where they may have important, even vital, consequences for the object of medical attention.

The inherited sources of inaccuracy can be classified as:

a) information about the patient, which can be divided into a number of categories, all of which have uncertainty.
b) medical history of patients, which is supplied by the patient, and is usually highly subjective and may include simulated, exaggerated, or understated symptoms; ignorance of previous diseases, failure to mention previous operations, and general recollection often leads to doubts about the patient medical history,
c) physical examinations, which the physicians conduct to obtain objective data. They are subject to mistakes and overlooking important indications, or may even fail to carry-out a complete test. Furthermore, they may misinterpret other indications because the boundary between normal and pathological status is not always clear.
d) results of laboratory tests are objective data, which depend on the accuracy of the measurements, organisational problems (mislabelling sample, wrong laboratory etc.), and even on the improper behaviour of the patient prior to the examination.

e) results of histological, X-ray, ultrasonic, and other clinical investigations which depend on correct interpretation by medical staff.

Section 2 surveys the use of fuzzy logic in medicine based on searches in medical data bases such as MEDLINE, INSPEC and edited books. The purpose of the study was to establish a roadmap which may help to forecast the future developments of fuzzy technology in medicine and healthcare. A simple search of the word "fuzzy" obtained many cited papers, in half of which the term was used to describe an unsharp border of structure or situation. For the rest, most of them recent ones, the word "fuzzy" was used as part of fuzzy sets or fuzzy logic. The main topics which were cited can be classified into 10 fields (each of which can be further classified into subheadings) as follows: conservative medicine, invasive medicine, regionally defined medical disciplines, neuro-medicine, image and signal processing, laboratory, basic science, nursing, healthcare and oriental medicine. In section 3, details of a particular application in anaesthesia are given.

2. FUZZY CONTROL AND MONITORING IN MEDICAL FIELDS

Imprecisely defined classes play an important role in human thinking. Fuzzy set theory derives from the fact that most natural classes and concepts are fuzzy rather than crisp nature. On the other hand, people can approximate well enough to perform many desired tasks. The fact is that they summarise from massive information inputs and still function effectively. For complex systems, fuzzy logic is quite suitable because of its tolerance to some imprecision. In the following sections a brief description is given of the key contribution which fuzzy control, estimation, and measurements technology have made in each of the topics which have been identified in a medical literature search.

2.1. CONSERVATIVE DISCIPLINES

Conservative medicine can be classified into the following disciplines: internal medicine, cardiology, invasive care, paediatry, endocrinology, oncology gerontology, and general practice. The literature search only found limited application of fuzzy control mostly in general practice and cardiology. Fuzzy logic is utilised for improved monitoring in pre-term infants (Wolf et al, 1996).

2.1.1. Invasive Medicine

The invasive medicine field involve surgery, orthopaedics, anaesthesia, and artificial organs. The field of surgery is very wide as many factors contribute to it such as diagnostics, image processing, pathophysiological reasoning, and anaesthesia control. In anaesthesia, many applications have been reported in the use of fuzzy logic to control drug infusion for maintaining adequate levels of anaesthesia, muscle relaxation, and patient monitoring and alarm. In the field of orthopaedics, there has been no reported application of fuzzy control.

The field of anaesthesia is where most of the applications of fuzzy control have been reported. It involves monitoring the patient vital parameters and controlling the drug infusion to maintain the anaesthetic level constant. It includes depth of anaesthesia (Abbod and Linkens, 1998), muscle relaxation (Linkens and Mahfouf, 1988; Westenskow, 1997), hypertension during anaesthesia (Oshita et al, 1993), arterial pressure control (Zbinden et al, 1995) and mechanical ventilation during anaesthesia (Schaublin et al, 1996), and post-operative control of blood pressure (Ying and Sheppard, 1994).

Different methods have been used which utilise fuzzy logic, the first being a real-time expert system for advice and control (RESAC) based on fuzzy logic reasoning (Greenhow et al, 1992). Later examples involve a basic fuzzy logic controller (Linkens and Mahfouf, 1988), self-organising fuzzy logic controller (Linkens and Hasnain, 1991), and hierarchical systems (Shieh et al, 1999).

Most of the fuzzy logic control applications in the field of artificial organs are concerned with artificial hearts. A fuzzy controller has been implemented for adaptation of the heart pump rate to body perfusion demand by pump chamber filling detection (Kaufmann et al, 1995). Another more advanced system based on neural and fuzzy controller for artificial heart was developed by Lee et al (1996). Future prospects for cardiac assist patients involving fuzzy logic was described by Mussivand (1998).

2.2. REGIONALLY DEFINED MEDICAL DISCIPLINES

There are different fields which belong to regionally defined medical disciplines: gynaecology, dermatology, dental, ophthalmology, otology, rhinology, laryngology and urology. Although there are many application fields, the literature search has only resulted in a single application of fuzzy inference to dental medicine. Although the application is not directly related to control, it utilises fuzzy inference for personal identification / sex determination from teeth (Takeuchi, 1993).

2.2.1. Neuromedicine

Neurology, psychology, and psychiatry are the sub-subjects of the neuromedicine field. The neurology sector did not score literature on fuzzy control. In psychology, there has been modelling of the functional status of a human operator based on fuzzy logic which is used to predict and evaluate the operators behaviour (Astanin, 1989). Also, fuzzy logic was used to analyse the effect of face expression on speech perception in direct communication (Massaro and Cohen, 1996). The prediction of patient response to new pharmacotherapies for alcohol dependence has been measured using fuzzy logic since it has been not successful using standard statistical techniques (Naranjo et al, 1997).

In the field of psychiatry, a complex psychiatric computer expert system, including functions that help the physicians and the hospital staff in the administrative, diagnostic, therapeutic, statistical, and scientific work has been developed (Kovacs and Juranovics, 1995).

2.2.2. Image and Signal Processing

Image and signal processing are mainly concerned with signal processing, radiation medicine, and radiology. The application of fuzzy control is divided into two sections, control and monitoring. Most of the applications have been concerned with signal processing. The first application is a combined fuzzy monitoring and control of the electrical and chemical responses of nerve fibres (al-Holou and Joo, 1997). Another application is the automation of matrix-assisted laser desorption/ionization mass spectrometry using fuzzy logic feedback control (Jensen et al, 1997). Fuzzy feedback control was implemented for artificial ventilation of lungs (Vasi'leva et al, 1989). On the monitoring side, fuzzy signal processing has been implemented in many applications such as sleep monitoring (Gath et al, 1983), monitoring of preterm infant (Wolf et al, 1996), clinical monitoring of disease progression (Steimann, 1996), and analysis of eyes movements (Allum et al, 1998).

Radiation medicine is mainly concerned with tumour monitoring and quantification. Fuzzy clustering is used to analyse magnetic images of tumour response to therapy (Vaidyanathan et al, 1997; Velthuizen et al, 1995). In another application, high energy radiotherapic images with poor quality, have used a fuzzy image enhancing process (Krell et al, 1998). Lastly, a two dimensional image restoration technique using fuzzy logic was developed for diagnostic and treatment planning for radiation therapy (Butt et al, 1998).

2.2.3. Laboratory

The only direct application of fuzzy control strategies was the application of pH-state to fed-batch cultivation of genetically engineered Escherichia coli. The control of the substrate concentration at an appropriate level was sought in order to avoid the accumulation of acetate, thereby elevating the expression level of plasmid-encoded protein (Jin et al, 1994).

Analysis and interpretation of laboratory data sets was the other indirect application of fuzzy logic. Two typical applications are: interpretation of pathophysiology by laboratory data (Shimizu et al, 1990), and analysis of the variations of clinical test data on fasting therapy using a fuzzy similarity dendrogram (He et al, 1991).

2.2.4. Basic Science

Basic science consists of different categories: medical information, anatomy, pathology, forensic medicine, genetics, physiology, pharmacology, and education. The use of fuzzy logic in medical informatics began in the early 1970s. Recent work on fuzzy controllers is more concerned with stability, self-organising, and synergies with other computing techniques such as neural network and genetic algorithms. Management and retrieval of information using fuzzy logic is one of the possible application discussed by Chiodo et al (1994).

In the fields of anatomy, pathology, forensic medicine and genetics, there are many application of fuzzy logic mostly based on image analysis and fuzzy clustering. In pathology, an expert system was used based on fuzzy logic for reasoning with uncertainties in selecting treatment strategy suitability (van Ginneken and Smeulders, 1991). In forensic medicine, fuzzy logic was used to personal identification (sex determination) from teeth (Takeuchi, 1993). In genetics, fuzzy logic has been used to develop control strategies for the application of pH-state to fed-batch cultivation of genetically engineered escherichia coli (Jin et al, 1994).

In pharmacology and biochemistry, fuzzy logic prediction was used for the rodnet carcinogenicity of organic compounds using a fuzzy adaptive least squares method (Moriguchi et al, 1996). In education, the use of fuzzy logic has different facets. Fuzzy mathematics was utilised for evaluating the teaching of students in a clinical setting (Chen, 1996). Evaluation of the self-taught ability of nursing administrators with fuzzy medicine was also reported (Wang and Sun, 1996).

2.2.5. Healthcare

There has been a growing interest in healthcare among many people. Some topics related to healthcare are: drinking water quality, driving fatigue, health risks in work environment (Genaidy et al, 1998), and healthcare organisations.

During the management process in health organisations, certain situations can arise when data necessary for decision-making is in fuzzy form. As an example, the problem of resource allocation among consulting rooms in the outpatient division of one hospital in Tbilisi was chosen. The aim is to minimise patients' queues as well as physicians' idle time (Kachukhashvili et al, 1995).

3. CONTROL OF DEPTH OF ANAESTHESIA

The field of Depth of Anaesthesia (DOA) is a very challenging area for fuzzy control since direct measurements are unavailable. Thus, a hierarchical structure containing fuzzy reasoning at every level is being developed. A previous system developed by Linkens et.al. (1994) based on fuzzy logic, called “SADA”, provided good control algorithms with self-learning capabilities, but only limited measurement inference based mostly on cardiovascular indicators (i.e. changes in blood pressure (BP) and heart rate (HR)). However, these changes are subject to influence by drugs used in anaesthesia (e.g. opioids and anticholinergics), by surgical situation or patient’s circumstance (e.g. fluid loss and blood loss), so they are unreliable. In the search for a reliable monitor of DOA the electroencephalogram (EEG) is an obvious signal to investigate. The EEG, generated from within the central nervous system (CNS), is not affected by neuromuscular blockers, and the raw signal has been known for some time to show graded changes with increasing concentration of anaesthetics. However, extensive research has proved disappointing because these changes vary for different agents and no unifying feature has been identified for measure of DOA in spite of extensive signal processing.

Attention, therefore, has turned to Evoked Potentials (EPs) in the EEG, in the search for a signal which reflects the subjective clinical signs that anaesthetists have used over the years to assess their patients during anaesthesia. The signal should show similar graded changes with anaesthetic concentration for different agents; show appropriate changes with surgical events; and indicate awareness or very light anaesthesia. The EPs, which are changes in electrical potential evoked by auditory, somatosensory or visual stimuli, have two advantages over the EEG in the study of anaesthesia: (a) the EP is an indication of the responsiveness of the CNS whereas the EEG reflects the resting level; (b) the EPs have anatomical significance. The auditory evoked potential (AEP) has been tested with the above criteria in mind (Thornton et.al, 1993). Thus, having validated the mid-latency auditory evoked potential (MLAEP) as a measure of depth of anaesthesia (Schwender et.al, 1994), we are now proceeding to test it in the clinical context. The main features of MLAER, which reflect the anaesthetic depth, are the changes in latencies and amplitudes of its waves. A digital signal processing (DSP) technique was carried out to smooth MLAER and improve the signal to noise ratio (S/N). Feature extraction has been implemented to extract the factors describing the changes in amplitudes and latencies of MLAER waves which are related to DOA. Three factors have been obtained and merged together using fuzzy logic to create a reliable index for DOA.

Previous research on closed-loop control has indicated that patients can be modelled and controlled better with Artificial Intelligence techniques such as fuzzy logic and neural network (Linkens, et.al., 1993, 1994). Muscle relaxation has been controlled using a fuzzy logic controller. Depth of anaesthesia is, however, more difficult to measure. Recent research on the measurements of DOA has concentrated on use of the AEP signal (Newton, et.al., 1992, Schwender, et.al., 1996). More recently, neural networks and fuzzy logic have been used to analyse the signal and measure the DOA (Webb, et.al., 1996). In recent work by the authors, the use of neural networks and fuzzy logic (Linkens, et.al., 1996) have been used to control the amount of infused drug using a rule-based fuzzy logic controller.

This paper describes the structure of a real-time measuring system based on fuzzy logic as shown in figure 1. The system uses neuro-fuzzy and multiresolution wavelet analysis for monitoring the DOA based on AEP signals. The measuring system uses a DSP signal processing chip hosted in a PC, providing averaging and analysis using multiresolution wavelet analysis. The analysed signal is fed to a neuro-fuzzy system where the inference takes place to obtain a measure for the DOA. Another measure for DOA is based on the cardiovascular system status using a rule-based fuzzy logic classifier. The two measures are merged together using rule-based fuzzy logic data fusion to decide the final DOA. Based on the classified DOA, a target concentration is decided by a rule-based fuzzy logic controller which feeds the target to a Target Controller Infusion algorithm (TCI). The patient is represented on a different machine using a mathematical model with numerical simulation. The system forms a closed-loop controller for monitoring the DOA for patients undergoing surgical operation.

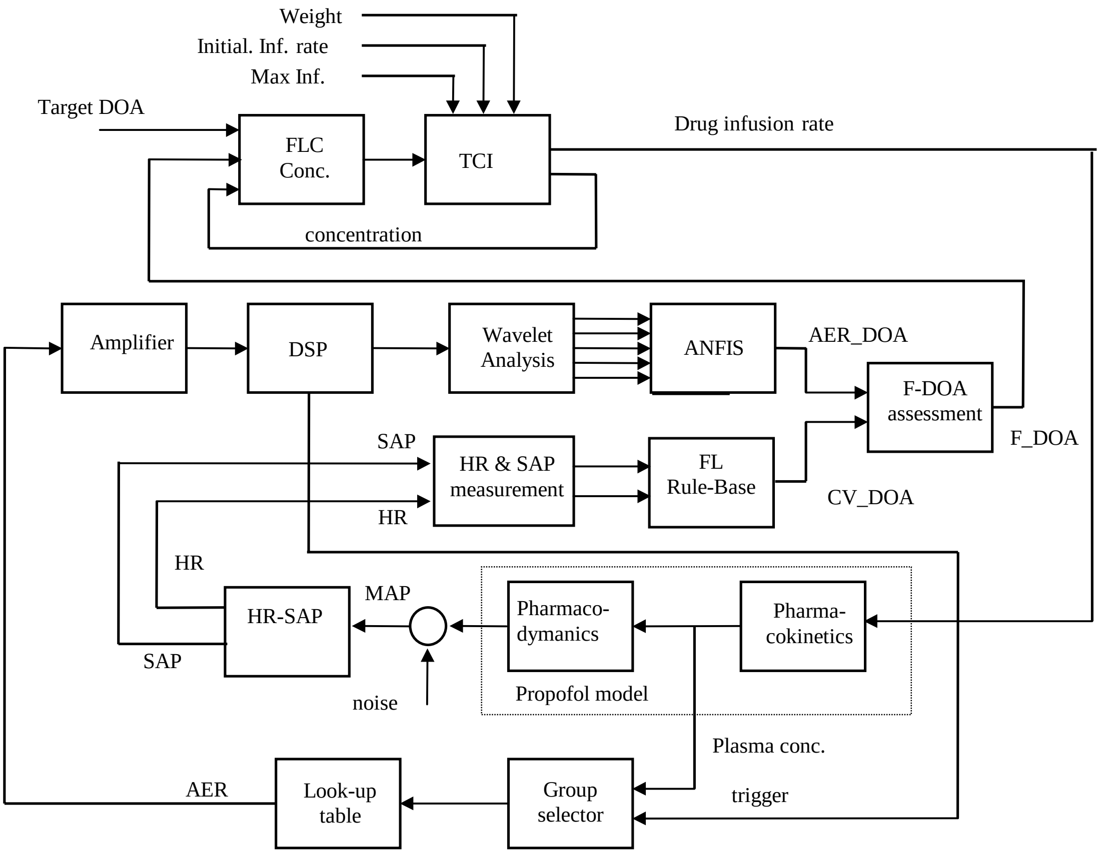


Figure 1: Block diagram of DOA control system

3.1. AUDITORY EVOKED RESPONSES FOR DOA ASSSESMENT (*AER_DOA*)

Depth of anaesthesia is measured via the evoked brain potentials which are measured using one or more scalp electrodes. The auditory evoked potentials (AEP) are the responses in the EEG to clicks applied to the ear. It can be recorded in operating theatre and extracted from the EEG by computer averaging. The signal is recorded using a computer fitted with a DSP card which produces the auditory stimulus in the patient’s headphone, and samples the EEG at 1 kHz for a sweep period of 120 ms after each click. The computer produces an average of 188 data sweeps plus calculation time, each 30 sec. A typical AEP signal can be classified into three sections: brain stem (0 - 15 ms), early cortical (15 - 80 ms), and late cortical (80 - 1000 ms). The response features comprise a number of peaks with different amplitudes and latencies. The peaks appearing in the early cortical section are labelled as Na, Pa, Nb, and Pb. A Pathfinder electrodiagnostic system has been used to record AEP signals using a 0.1 ms click duration at a 6.122 Hz stimulating frequency. A study carried out by Schwender et.al. (1996) measured latencies of the peaks V, Na, Pa, Nb, and Pb (ms) and amplitudes Na/Pa, Pa/Nb, and Nb/Pb (V). The AER signals were recorded for awake and sleep patients. A grand average was calculated for different levels of anaesthesia for constant level of anaesthetic drug, showing the relationships which exist between DOA and latencies.

3.1.1. AER Signal Muliresolution Wavelet Analysis

One of the methods of analysing the AEP signal is the of Fourier Transform (FT). Schwender et.al. (1994) have used it for the analysis of MLAEP to find the region corresponding to the maximum power in the frequency spectrum as a means to identify the major oscillatory components in the signal. They showed that an increase in the DOA yields a shift in the power spectrum of the oscillatory component along with an attenuation in the response. The shortcoming of FT is that it can not represent the transient nature of the peaks in the signal. However, the Wavelet Transform (WT) has the ability to deal with non-stationary signals, as well as the ability to decompose the signal into its frequency components, allowing the identification of major oscillatory components.

3.1.2. ANFIS for Classifying AER Based DOA

The Adaptive Network Based Fuzzy Inference System (ANFIS) architecture and learning is based on a fuzzy inference system implemented in a framework of an adaptive network (Jang, 1993). Using a hybrid learning procedure, ANFIS can learn an input-output mapping based on human knowledge (in the form of if-then fuzzy rules). The ANFIS architecture has been employed to model non-linear functions, identify non-linear components on-line in a control system, and predict a chaotic time series.

ANFIS performs the identification of an input-output mapping, available in the form of a set of N input-output examples, with a fuzzy architecture, inspired by the Takagi-Sugeno modelling approach (Bersini et.al., 1995). The fuzzy architecture is characterised by a set of rules, which are properly initialised and tuned by a learning algorithm. The rules are in the form:

1) if input1 is A11 and input 2 is A12 then output =f1(input1,input2)

2) if input1 is A21 and input 2 is A22 then output =f2(input1,input2)

where Aij are parametric membership functions.

3.1.3. ANFIS Classifier System Training

Multiresolution Wavelet Analysis was used to obtain the coefficients of the Detail components D1-D4 of the AEP. A 5-point weighted moving average was used to smooth the data; it was observed that this weighted moving average did not add any noticeable delay in the signal (Linkens et al, 1997a, 1997b). These wavelet coefficients were then used to calculate the average energy in each of D1, D2, D3_1, D3_2, D3_3 and D4. The notes taken down during the course of the surgical procedure were then used to label the features. These features were furthermore labelled with the anaesthetist's expert opinion (based on the clinical signs of anaesthesia and his experience) on the DOA at different stages of the surgical procedure. Thus, labelling of the data could be carried out. Six labels, corresponding to distinct anaesthetic depths were used: *awake, light, ok_light, ok, ok_deep*, and *deep*. The data outliers were removed and the remaining data were normalised to zero mean and unit variance for each of the six categories. The data from nine patients were used to create a training and a validation set. 1131 data point were used in the training and validation session.

3.2. FUZZY LOGIC RULE-BASED CLASSIFIER FOR CV BASED DOA (CV_DOA)

The *CV_DOA* classifier is based on two inputs, namely HR and SAP and the output is the DOA. The input variables can be classified into three linguistic levels for each variable, *low, medium*, and *high*. Medium means the input variable is within the normal range, low and high mean below or above the normal range respectively. In contrast, the output variable (DOA) has six linguistic levels, *deep, ok_deep, ok, ok_light, light, and awake* as shown in Table 1. Details of the rule-base derived from anaesthetists' experience have been reported in a previous study by Linkens et.al. (1996).

		SAP		
	CV_DOA	*high*	*medium*	*low*
HR	*high*	awake	ok_light	ok
	medium	light	ok	ok_deep
	low	ok	ok_deep	deep

Table1: *CV_DOA* classifier rule-base.

3.3. FUZZY LOGIC RULE-BASED DATA FUSION FOR MERGING AER_DOA AND CV_DOA

The last junction is to merge the to classified DOA measured from the previous agents (*AER_DOA* and *CV_DOA*) to produce a final DOA(*F_DOA*) using rule-based fuzzy logic data fusion. As mentioned in the last two sections, each variable has 6 linguistic levels. The same structure will be used for the output measure of DOA. The rule-base for merging the two measures is shown in Table 2.

		AER_DOA					
	F_DOA	*awake*	*light*	*ok_light*	*ok*	*ok_deep*	*deep*
CV_DOA	*awake*	awake	awake	light	light	ok_light	ok
	light	awake	light	ok_light	ok_light	ok	ok
	ok_light	light	ok_light	ok_light	ok	ok	ok_deep
	ok	ok_light	ok	ok	ok	ok	ok_deep
	ok_deep	ok_light	ok	ok	ok	ok_deep	deep
	deep	ok	ok	ok_deep	ok_deep	deep	deep

Table 2: F_DOA classifier rule-base.

3.4. TARGET CONTROLLER INFUSION (TCI)

The TCI system was first introduced by Alvis and co-workers (Alvis et.al., 1985) who controlled fentanyl infusion during anaesthesia. The idea behind the system is to keep the plasma concentration level constant. In order to do that, the infusion rate has to be determined. Once the desired level is reached, the system maintains the concentration in an open-loop manner

The TCI system used in this study is based on a three-compartment patient model and uses the pharmacokinetic parameters used by Glass et.al. (1989). The three compartment pharmacokinetic model of the patient as well as the pharmacokinetic parameters (in min-1) describes the flow rate of the drug between the various compartments. K10 is the rate constant for elimination from the central compartment, K_{12} is the rate constant for drug transfer from the central compartment to compartment 2, K_{13} is the rate constant for drug transfer from the central compartment to compartment 3, K_{21} is the rate constant for drug transfer from the compartment 2 to the central compartment and K_{31} is the rate constant for drug transfer from the compartment 3 to the central compartment. The values of the pharmacokinetic parameters describing the patient model are shown in Table 3.

V_1 (litres Kg^{-1})	K_{10} (min^{-1})	K_{12} (min^{-1})	K_{13} (min^{-1})	K_{21} (min^{-1})	K_{31} (min^{-1})
0.159	0.152	0.207	0.040	0.092	0.0048

Table 3: V1 is used to derive Vc, the volume of the central compartment (also sometimes referred to as compartment 1) from the mass of the patient using the equation Vc = mass $\times$ 0.159 (Glass et.al., 1989).

The three-compartment model described here is a linear model since the pharmacokinetic parameters describing the model are constant. The rate of transfer of the drug from one compartment to another is proportional to the amount of drug present in the first compartment.

3.5. CLOSED-LOOP SYSTEM FOR CONTROL OF DOA

The system has been implemented on two computers, one acting as the controller and the other acting as the patient simulator. The controller computer is used as a host for the DSP chip card for recording the AER signal. In the meantime, its used for analysing the signal, recording heart rate and blood pressure, and the associated calculation regarding DOA. The TCI system is also implemented on the controller computer for calculating the amount of the infused drug. In some of the latest syringe driver systems, a TCI system is installed on board the device, in which case the TCI system would not be required.

On the simulator computer, the patient model is simulated using a 4th order Runge-Kutta algorithm in two parts, the pharmacokenetic model and the pharmacodynamic model. The output of the pharmacodymanic model is the plasma concentration which is fed to two paths, the first path is to the pharmacodynamic model block (effect compartment) then to the non-linear effect block (Hill equation). This output is the mean arterial pressure which is fed in turn to two more blocks, to calculate the associated systolic pressure, and the heart rate. The second path is to the AER signal simulation block which consists of a look-up table for the AER signal classified based on the plasma concentration from nine patients. According to the plasma concentration calculated by the model, a certain group is selected which is related to the present plasma concentration, then a single AER trace is selected randomly from ten stored traces. Each trace consists of 120 data points sampled at 100msec. The selected trace is used as an output AER signal via DA converter. The AER signal is released on the reception of the trigger signal from the AER system amplifier which is used in reality for the earphone trigger.

The input to the simulator is the infused drug calculated by the controller computer via an AD converter. The final output of the simulator is SAP and HR at 30 second update intervals. The AER signal is sampled at 120msec for each trace.

The controller computer is connected to the DSP chip board which its aim is to collect the AER signal via the amplifier board as well as providing the auditory trigger signal at 6.122Hz rate. 188 sweeps are collected each of 120msec, and by the end of the collection the data are averaged and filtered to produce the final AER signal every 30 sec. Other measurements are recorded such as the heart rate and systolic blood pressure each 30 sec, therefore the whole system sampling rate is 30 second.

After collecting the AER signal, it is fed to the wavelet analysis block to analyse the required components of the signal then fed to the ANFIS block where the AER_DOA is calculated. In the meantime the recorded HR and SAP are fed to the fuzzy logic rule-base for analysis of CV_DOA. Prior to that both SAP and HR are filtered using a weighted moving average filter. The last stage in DOA analysis is to feed CV_DOA and AER_DOA to the final DOA analysis block. The calculated F_DOA is fed to the next block in the system which is the plasma concentration controller block. Based on the current target concentration and the measured DOA, a new target concentration is calculated using a fuzzy logic rule-based controller. The target concentration controller consists of three rule-bases. One rule-base is selected depending on the required DOA level. The three levels are ok_light, ok, and ok_deep.

The plasma target concentration is fed to the TCI block which is based on the initial information supplied. It calculates the drug infusion rate and feeds it to the syringe driver which in our case will be the simulator via a DA converter. The initial settings for the TCI algorithm are based on the patient weight, maximum infusion rate, and the initial infusion rate.

3.6. SIMULATION RESULTS

Simulation runs were conducted for different patients: nominal patients with three different weights, a sensitive patient, and a resistive patient The type of AER signal used in the simulator and the random selection gives the phenomenon of a random component in the AER signal, as well as the inherited noise through the amplified AER.

The following parameters were used during the simulation run reported here:

Patient weight 60 Kg

Propofol Concentration 10000 ng ml-1

Maximum Infusion Rate 6000 mg hr-1

HR base line 70 BPM.

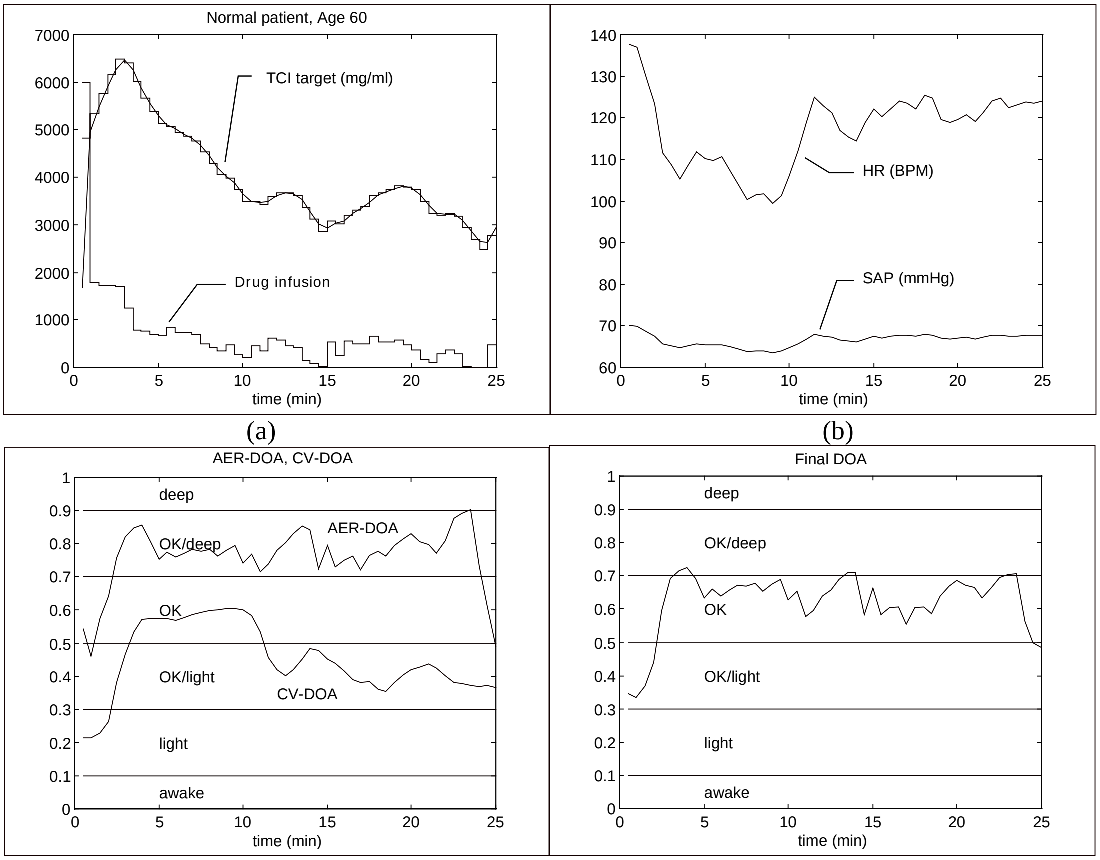
SAP base line 140 mmHg.

Patient Sensitivity (gain) Normal: 6.58

Moving average filter used for HR, SAP, AER_DOA, CV_DOA, and F_DOA.

In the simulation run graphs, each figure is divided into four subplots: the target, central compartment concentration, and the infused drug are shown in the first plot (a). The second plot (b) shows the heart rate and blood pressure, the third plot (c) shows the classified AER_DOA and CV_DOA, while the last plot (d) shows the final DOA as the two intermediate DOAs are merged together.

A simulation case is shown in figure 2, the simulated condition of the patient being in steady state for the whole period. AER_DOA had a deeper level of anaesthesia than CV_DOA, but the final level after merging was in the ok level, as required by the input command signal.



(a) (b) (c) (d)

Figure 2: simulation run for a nominal 60 Kg patient

3.7. CLINICAL TRIALS

The system is being used on-line in the operating theatre for clinical trials in the Royal Hallamshire Hospital, Sheffield. This procedure required connecting the system to a Datex device for recording HR and BP, as well as a Graseby 3400 syringe pump via the RS232 serial port.

The procedure for using the system starts when the patient is brought to the anaesthetic induction room, prior to the operating theatre. The anaesthetic room is equipped with a Datex AS/3 machine, which measures the blood pressure and heart rate, meanwhile, there is another Datex AS/3 machine in the operating theatre. At the start, the system is connected to the Datex machine in the anaesthetic room, together with the Graseby pump. The AER system is linked to the patient by connecting the probes to the forehead and to the back of the ears after cleaning the contact areas, while the earphones are placed in the patient's ears.

When starting the system, the first stage is calibration, when signals are recorded from the patient while he is awake, and the skin conductivity, including the probes, is measured. A threshold level is set to either accept the probes connection or to re-do it. The second stage is to record an offset level for the system recordings. Following these two stages, the system will be ready for infusion. After injecting the drug fentanyl, the anaesthetist decides a TCI level for the drug propofol, and then starts the infusion stage. The infusion stage is initiated by the computer after pressing the start infusion key. After a while the patient will be anaesthetised which can be monitored from the DOA measure on the PC.

When the patient is anaesthetised adequately, he is moved to the operating theatre, during which the Datex measurements system is halted, the RS232 cable is disconnected from the Datex AS/3 machine and reconnected to the other machine in the theatre. A special key has been designated to this procedure in order to stop the Datex readings and re-initiate then after being re-connected. The other equipment, i.e. the syringe pump and AER amplifier box are moved with the patient to the theatre.

Once in the theatre, the anaesthetist can either chose an advisory mode or automatic infusion mode. The former mode gives advice to the anaesthetist on the recommended TCI level based on the current level of DOA. This advice can either be ignored or accepted, depending on the anaesthetist’s judgement. The latter mode is based on feedback control to maintain a constant level of DOA. During the operating procedures, many events can take place including the infusion of other drugs, such as muscle relaxants which interferes the blood pressure and heart rate indication of DOA. Also the use of a diathermy machine has a large effect on the AER signal causing saturation.

The result of a clinical trial involving a small incision cholecystectomy plus operative cholangiogram is shown in Figure 3. The patient details are given below:

Patient Name: BG

Sex: Male

Weight: 59 kg

Date of Birth: 17-9-1937 (Age: 61)

Blood Pressure: 152/77

Heart Rate: 66

Operation Type: Small incision cholecystectomy plus operative cholangiogram

Anaesthesia: start with 200 µg fentanyl, 35 mg atracurium, propofol was started at 4000 mg/ml.

Estimated recovery time = 11.4 min

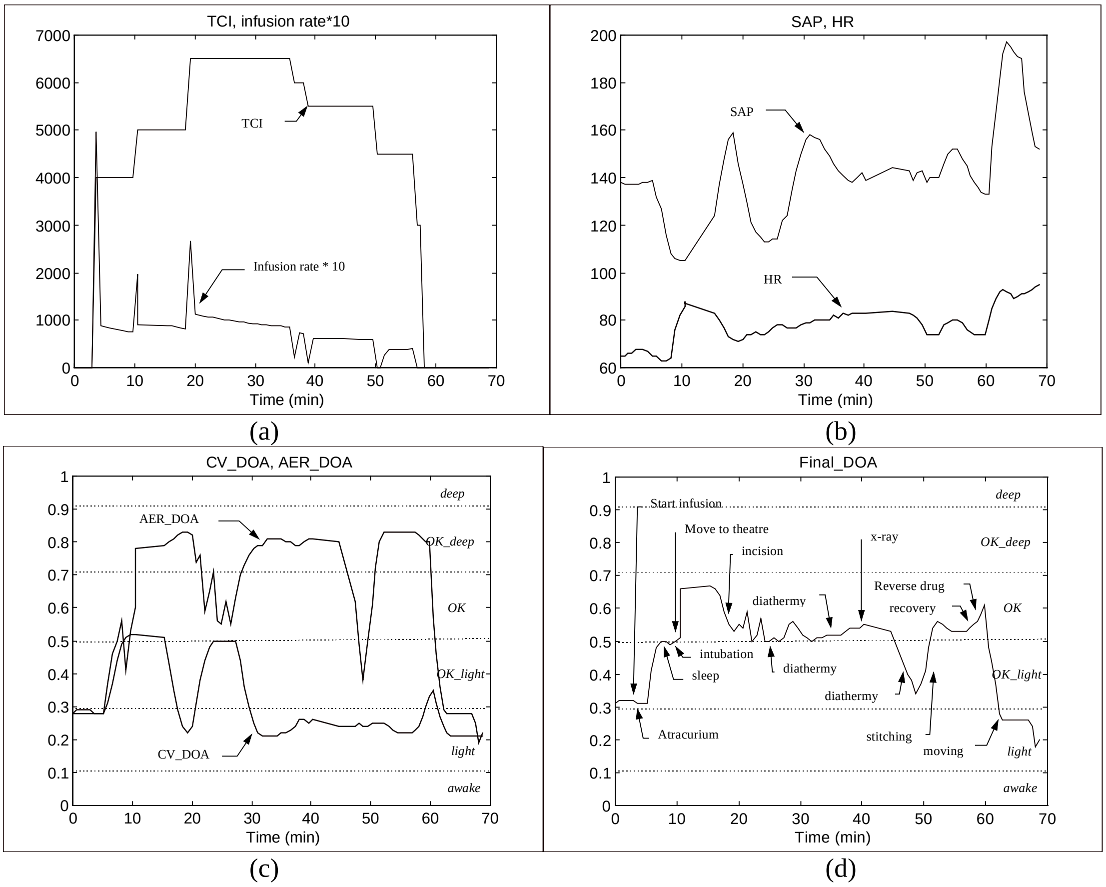


Figure 3: Time response for a clinical trial (patient BG).

The anaesthesia procedure started with the infusion of 200 μg fentanyl followed by oxygen administration. The propofol infusion was started after 4 minutes at 4000 mg/ml target concentration. The effect of the drug was shown by a depression change in blood pressure and heart rate which indicated an ok level of the CV_DOA and an ok_deep for AER_DOA. The patient went to sleep and intubation took place. After 11 minutes the patient moved to the theatre where the Datex machine was disconnected and reconnected to the operating theatre Datex machine. When the incision was made, the blood pressure and heart rate increased which indicated a low level of CV_DOA, this being compensated by the AER_*DOA* such that the final *DOA* was kept in the *ok* region. The operation went smoothly except for two occasions when diathermy occurred, the *AER_DOA* then indicating *ok_light*. At the end of the operation the infusion was stopped and recovery occurred after 10 minutes, which was near to the estimated recovery time (11.7 min).

4. CONCLUSIONS

Based on this study, future developments of fuzzy technology in medicine and healthcare can be tentatively forecast. The sectors of medical activities can be brought together in a hierarchical scheme according to the mode of the medical procedure. This means that significant methodologies, relationships and demands are correlated. This scheme substantiates the hypothesis that a successful application in one sector should lead to a successful application in neighbouring sectors. All information gathered in this study retain their time value. The papers are arranged on a time scale. This means that not only the actual state of the art, but also the dynamic process of the information spread in each sector can be determined. This two dimensional representation is useful in the prediction of future events. It suggests that in 2 to 3 years the spread of fuzzy logic applications will follow the tendencies of recent years. Table 4 summaries the number of application of fuzzy logic for each criteria classified on a yearly basis based on two databases: MEDLINE and INSPEC. Each database is different, since MEDLINE mainly reviews medical journal papers, whereas, INSPEC reviews computer science journals and conferences papers. It is noticeable that, however, there is a surprisingly limited intersection between the two databases which grows as the number of publications increases. A notable exception is Adlassnig (2000) who is well known in both fields. Nevertheless, the two databases are correlated, as there is an increase in the number of publications as the year scale progresses.

From such an analysis, some tentative conclusions are:

1. Internal medicine, anaesthesia, radiology, electrophysiology, pharmacokinetics, and neuromedicine already use fuzzy logic methods to a considerable degree. Such techniques are: fuzzy expert systems, fuzzy control, fuzzy signal and image processing, fuzzy modelling, and fuzzy neural simulation. Table 5 shows a breakdown of such techniques across the medical sub-disciplines.
2. In the field of surgical disciplines, dental medicine, general practice, and nursing, there are no specific applications to date.
3. Most regionally defined medical disciplines are developed from methods used in neighbouring disciplines.
4. Papers in the field of medical reasoning and decision support sciences are growing rapidly in number. This will keep developments in other sectors growing.

Although the literature search was not exhaustive, it is sufficient to illustrate the main features governing the penetration of fuzzy technology into the medicine and healthcare aspects of the life sciences. It is hoped that the survey will prompt the identification of matching techniques and subject areas where further exploitation of fuzzy systems may be both feasible and timely.

A closed-loop control system for monitoring and control of depth of anaesthesia has been developed based on two different measures, the AER system and the cardiovascular system. The system aims to provide more reliable measurements of DOA than has been achieved via manual and other approaches.

The system has been validated for three different patients sensitivities: nominal, sensitive, and resistive. A simulation study using a numerical model of the patient shows that the closed-loop system effectively maintains the patient at the clinically acceptable anaesthetic depth even when the stimuli reflect those of real surgical procedures. Furthermore, the system has been tested in clinical trials for measuring the depth of anaesthesia during operations. Although it was used only in advisory mode, it proved to be reliable and gave good indications of the level of DOA. More validations tests are scheduled to be carried out in preparation for closed-loop control mode investigations.

5. ACKNOWLEDGEMENTS

The authors acknowledge financial support from the UK Engineering and Physical Science Research Council, and Professor D.G. Keyserlingk's contribution to the ERUDIT Roadmap.

Publication year	<89	90	91	92	93	94	95	96	97	98
Conservative disciplines										
internal medicine	-	-	-	-	1	-	-	-	1	-
cardiology	-	-	-	-	-	2	2	-	2	3
intensive care	1	-	-	-	-	1	-	-	-	1
paediatry	-	-	-	-	-	-	-	-	-	-
endocrinology	-	-	-	-	-	-	-	-	-	-
oncology	-	-	-	-	-	1	2	-	2	1
gerontology	-	-	-	-	1	-	-	2	2	2
general practice	1	1	-	-	1	1	1	2	4	2
Invasive medicine										
surgery	-	-	-	-	2	1	-	2	3	1
orthopaedics	-	-	-	-		1	-	1	-	-
anaesthesia	4	1	1	4	4	4	2	5	7	2
artificial organs	-	-	-	-	-	-	2	2	5	3
Regionally defined medical disciplines										
gynaecology	-	-	-	-	-	-	-	-	-	-
dermatology	-	-	-	-	-	-	-	-	-	-
dental medicine	-	-	-	-	-	1	-	-	-	-
ophthalmology	-	-	-	-	-	-	-	-	-	-
otology, rhinology etc	-	-	-	-	-	-	-	-	-	-
urology	-	-	-	-	-	-	-	-	-	-
Neuromedicine--										
neurology	-	-	-	-	-	-	-	-	-	-
psychology	-	-	-	-	1	-	1	2	1	2
psychiatry	-	-	-	-	-	-	1		-	-
Image and signal processing										
Signal processing	1	-	-	-	-	1	1	2	2	2
radiation medicine	-	-	-	-	-	-	-	-	-	-
radiology	-	-	-	-	-	-	-	1	1	-
Laboratory										
biochemical & tests	3	1	-	-	1	1	-	-	-	-
Basic science										
medical information	2	-	2	1	2	4	1	1	1	-
anatomy, pathology etc	-	1	-	-	2	1	2	-	1	2
physiology	1	-	-	-	-	-	-	-	1	-
pharmacology	1	-	-	-	1	-	-	-	1	-
education	1	-	-	-	1	1	-	-	1	1
Nursing	-	-	-	-	-	-	1	-	-	-
Healthcare	1	-	-	-	-	-	2	-	1	1

Table 4: Number of fuzzy technology publications applied in each medical sectors based on time scale.

	C-L	O-L	PID	Iden	M-B	Adp	Mnt	Class	S-L	Hyb
Conservative disciplines										
internal medicine	-	-	-	-	-	-	-	2	-	-
cardiology	-	-	-	-	1	2	2	2	-	2
intensive care	1	-		-	2	-	-	-	-	-
paediatry	-	-	-	-	-	-	-	-	-	-
endocrinology	-	-	-	-	-	-	-	-	-	-
oncology	1	-	-	-	-	-	2	1	-	2
gerontology	-	-	-	2	1	-	1	2	-	1
general practice	3	-	-	1	3	1	-	3	-	2
Invasive medicine										
surgery	3	-	-	-	2	-	2	-	-	2
orthopaedics	-	1	-	-	-	-	-	-	-	1
anaesthesia	18	2	3	-	1	4	-	-	3	3
artificial organs	7	-	-	-	-	1	-	2	-	2
Regionally defined medical disciplines										
gynaecology	-	-	-	-	-	-	-	-	-	-
dermatology	-	-	-	-	-	-	-	-	-	-
dental medicine	-	-	-	-	-	-	-	1	-	-
ophthalmology	-	-	-	-	-	-	-	-	-	-
otology, rhinology etc	-	-	-	-	-	-	-	-	-	-
urology	-	-	-	-	-	-	-	-	-	-
Neuromedicine										
neurology	-	-	-	-	-	-	-	-	-	-
psychology	-	-	-	-	1	-	2	3	-	1
psychiatry	-	-	-	-	1	-	-	-	-	-
Image and signal processing										
Signal processing	-	-	-	-	2	-	2	3	-	2
radiation medicine	-	-	-	-	-	-	-	-	-	-
radiology	-	-	-	-	-	-	-	2	-	-
Laboratory										
biochemical & tests	-	-	-	-	-	-	-	4	-	2
Basic science										
medical information	-	2	-	-	4	2	3	2	-	2
anatomy, pathology etc	-	3	-	3	1	-	-	2	-	-
physiology	-	-	-	-	2	-	-	-	-	-
pharmacology	3	-	-	-	-	-	2	-	-	-
education	-	2	-	-	2	-	1	-	-	-
Nursing	-	-	-	-	-	-	-	1	-	-
Healthcare	-	1	-	-	2	-	1	1	-	-

Table 5: Type of fuzzy technology application within each medical field.

Notation: C-L: closed-loop, O-L: open-loop, PID: proportional-integral-derivative, Iden: identification, M-B: model based, Adp: adaptive control, Mnt: monitoring, Class: classification, S-L: self-learning, Hyb: hybrid controllers.

REFERENCES

1. Abbod MF, Linkens DA, 1998. “Anaesthesia monitoring and control using fuzzy logic fusion”. Journal of Biomedical Engineering - Applications, Basis & Communications, Special Issues on “Control Methods in Anaesthesia”, Taiwan, August 1998.

2. Adlassnig KP, (ed), 2000, “Fuzzy diagnostic and theraputic decision support”, ERUDIT Workshop Proceedings, Vienna, May 11-12.
3. Allum JH, Honegger F, Troescher M, 1998. “Principles underlying real-time nystagmus analysis of horizontal and vertical eye movements recorded with electro-, infra-red-, or video-oculographic techniques”. J Vestib Res, 8(6), 449-463.
4. Alvis JM, Reves JG, Spain JA, Sheppard LC, 1985. “Computer assisted continuous infusion of the intravenous analgesic fentanyl during general anaesthesia - an interactive system”. IEEE Trans. on Biom. Eng., BME-32(5), 323-329.
5. Astanin SV, 1989. “A complex approach to modelling the functional status of a human operator based on the theory of fuzzy sets”. Kosm Biol Aviakosm Med, 23(4), 29-33.
6. Bersini G, Bontempi C, Decaestecker, 1995. “Comparing RBF and fuzzy inference systems on theoretical and practical basis”, in F.Fogelman-Soulie', P. Gallinari (Eds.) ICANN '95,International Conference on Artificial Neural Networks, Paris , 1, 169-174
7. Butt A, Acharya R, Sibata C, Shin KH, 1998, “Surface matching of multimodality image volumes by a fuzzy elastic registration technique”. Comput Med Imaging Graph, 22(1), 13-23.
8. Chen GH, 1996. “Use of fuzzy mathematics to evaluate the teaching of students in the clinical setting”. Chung Hua Hu Li Tsa Chih, 31(11), 658-660.
9. Chiodo F, Menditto A, Ouane-Keita F, Caroli S, 1994. “The management of information: storage and retrieval of data”. Ann Ist Super Sanita, 30(4), 433-437.
10. Gath I, Bar-On E, Rogowski Z, Bental E, 1983. “Automatic scoring of polygraphic sleep recordings: midazolam in insomniacs”. Br J Clin Pharmacol, 16(l), 89S-96S.
11. Genaidy AM, Karwowski W, Christensen DM, Vogiatzis C, Deraiseh N, Prins A, 1998. “What is 'heavy'?”. Ergonomics, 41(4), 420-432.
12. van Ginneken AM, Smeulders AW, 1991. “Reasoning in uncertainties. An analysis of five strategies and their suitability in pathology”. Anal Quant Cytol Histol, 13 (2), 93-109.
13. Glass PS, Goodman DK, Ginsberg B, Reeves JG, Jacobs JR, 1989. “Accuracy of pharmacokinetic model-driven infusion of propofol”. Anesthesiology, 71(3A), A277.
14. Greenhow SG, Linkens DA, Asbury AJ, 1992. “Development of an expert system advisor for anaesthetic control”. Comput Methods Programs Biomed, 37(3), 215-229.
15. He YX, Hu YQ, Yu QF, Tang ZJ, 1991.”Characteristics of different isolates of schistosoma japonicum from china in the final hosts”. Southeast Asian J Trop Med Public Health, 22(2), 240-244.
16. al-Holou N, Joo DS, 1997. “evelopment of a fuzzy logic based system to monitor the electrical responses of nerve fibre”. Biomed Sci Instrum, 33, 376-381.
17. Jang JR, 1993. “ANFIS: Adaptive-network, based fuzzy inference system”. IEEE transaction on Systems, Man, and Cybernetics, 23(3), 665-685.
18. Jensen ON, Mortensen P, Vorm O, Mann M, 1997. “Automation of matrix-assisted laser desorption/ionisation mass spectrometry using fuzzy logic feedback control”. Anal Chem, 69(9), 1706-1714.
19. Jin S, Ye K, Shimizu K, 1994. “Efficient fuzzy control strategies for the application of pH-state to fed-batch cultivation of genetically engineered escherichia coli”. J Chem Technol Biotechnol, 61(3), 273-281.
20. Kachukhashvili GS, Tsiskarishvili NE, Dubovik MV, Badiashvili GV, 1995. “The use of fuzzy sets techniques in managing health organisations”. Medinfo, 8, Pt 1, 541.
21. Kaufmann R, Becker K, Nix C, Reul H, Rau G, 1995. “Fuzzy control concept for a total artificial heart”. Artif Organs, 19(4), 355-361.
22. Kovacs M, Juranovics J, 1995. “"Auctoritas" psychiatric expert system shell”. Medinfo, 8 Pt 2, 997.
23. Krell G, Tizhoosh HR, Lilienblum T, Moore CJ, Michaelis B, 1998. “Enhancement and associative restoration of electronic portal images in radiotherapy”. Int J Med Inf, 49(2), 157-171.
24. Lee M, Ahn JM, Min BG, Lee SY, Park CH, 1996. “Total artificial heart using neural and fuzzy controller”. Artif Organs, 20(11), 1220-1226.
25. Linkens DA, Abbod MF, Backory JK, 1996. “Fuzzy logic control of depth of anaesthesia using auditory evoked responses”. IEE Colloquium on Fuzzy Logic Controller in Practice, IEE Savoy Place, London, 15 Nov, pp 4/(1-6).

26. Linkens DA, Abbod MF, Backory JK, 1997a. “Closed-loop control of anaesthesia using a wavelet-based fuzzy logic system”, EUFIT’97, Aachen, Germany, September 8-12.
27. Linkens DA, Abbod MF, Backory JK, 1997b. “Auditory evoked responses for measuring depth of anaesthesia using a wavelet fuzzy logic system”. Control Engineering Practice, 5(12), 1717-1726. .
28. Linkens DA and Hasnain SB, 1991. “Self-organising fuzzy logic control and its application to muscle relaxation anaesthesia”. IEE Proc PtD, Control Theory and Applications, 138, 274-284.
29. Linkens DA, Mahfouf M, 1988. “Fuzzy logic knowledge based control of muscle relaxation”. IFAC Proc on Modelling and Control of Systems, Venice, Italy, 185-190.
30. Linkens DA, Mahfouf M, Peacock JE, 1993. “Propofol induced anaesthesia: a comparative control study using a derived pharmacokinetic-pharmakodynamic model”. Internal report, Department of Automatic Control and Systems Engineering, University of Sheffield.
31. Linkens DA, Shieh JS, Peacock JE, 1994. “Machine learning rule-based fuzzy logic control for depth of anaesthesia”. IEE Control ’94, 31-36.
32. Massaro DW, Cohen MM, 1996. “Perceiving speech from inverted faces”. Percept Psychophys, 58(7), 1047-1065.
33. Moriguchi I, Hirano H, Hirono S, 1996. “Prediction of the rodent carcinogenicity of organic compounds from their chemical structures using the FALS method”. Environ Health Perspect, 104(5), 1051-1058.
34. Mussivand T, 1998. “Future prospects for cardiac assist patients”. Int J Artif Organs, 21(3), 129-130.
35. Naranjo CA, Bremner KE, Bazoon M, Turksen IB, 1997. “Using fuzzy logic to predict response to citalopram in alcohol dependence”. Clin Pharmacol Ther, 62(2), 209-224.
36. Newton DEF, Thornton C, Konieczko KM, Jordan C, Webster NR, Luff NP, Frith CD, Dore CJ, 1992. “Auditory evoked response and awareness: a study in volunteers at sub-mac concentration of isoflurane”. British Journal of Anaesthesia, 69, 122-129.
37. Oshita S, Nakakimura K, Kaieda R, Murakawa T, Tamura H, Hiraoka I, 1993. “Application of the concept of fuzzy logistic controller for treatment of hypertension during anaesthesia”. Masui, 42(2), 185-189.
38. Shieh JS, Abbod MF, Linkens DA, Peacock JE, 1999. “Peacock JE, Hierarchical fuzzy-based support system for anaesthesia monitoring and control”. Proc. IEE PtD, Control Theory and Applications, in press.
39. Schaublin J, Derighetti M, Feigenwinter P, Petersen-Felix S, Zbinden AM, 1996. “Fuzzy logic control of mechanical ventilation during anaesthesia”. Br J Anaesth, 77(5), 636-641.
40. Schwender D, Kaiser AD, Klasing S, Peter K, Poppel E, 1994. “Midlatency auditory evoked potentials and explicit and implicit memory in patients undergoing cardiac surgery”. Anaesthesiology, 80, 493-501.
41. Schwender D, Klasing S, Conzen P, Finsterer U, Poppel E, Peter E, 1996. “Midlatency auditory evoked potentials during anaesthesia with increasing endexpiratory concentrations of desflurane”. Acta Anaesthesiologica Scandinavica, 40(2), 171-6.
42. Shimizu H, Haida M, Niwa M, 1990, “Interpretation of pathophysiology by laboratory data (3). A consultation program based on clinical laboratory data”. Tokai J Exp Clin Med, 15(1), 51-79.
43. Steimann F, 1996. “The interpretation of time-varying data with DIAMON-1”. Artif Intell Med, 8(4), 343-357.
44. Sun Y, Kohane I, Stark AR, 1994. “Fuzzy logic assisted control of inspired oxygen in ventilated new-born infants”. Proc Annu Symp Comput Appl Med Care, 756-761.
45. Takeuchi T, 1993. “Application of fuzzy inference to personal identification--sex determination from teeth”. Nippon Hoigaku Zasshi, 47(3), 239-249.
46. Thornton P, Creagh-Barry C, Jordan, Newton DEF, 1993. “Anaesthetic depth and auditory evoked potentials”. Acta. Anaesthesiol. Scand., 37 (S100): 105-108.
47. Vaidyanathan M, Clarke LP, Hall LO, Heidtman C, Velthuizen R, Gosche K, Phuphanich S, Wagner H, Greenberg H, Silbiger ML, 1997. “Monitoring brain tumour response to therapy using MRI segmentation”. Magn Reson Imaging, 15(3), 323-334.
48. Vasi'leva OI, Ionov IP, Kantor PS, U'lianov SV, 1989. “Dual control of artificial ventilation processes of the lungs using a fuzzy regulator in the feedback circuit”. Med Tekh, 1, 11-21.
49. Velthuizen RP, Clarke LP, Phuphanich S, Hall LO, Bensaid AM, Arrington JA, Greenberg HM, Silbiger ML, 1995. “Unsupervised measurement of brain tumour volume on MR images”. J Magn Reson Imaging, 5(5), 594-605.

50. Wang RH, Sun ZQ, 1996. “Evaluation of self-taught ability of nursing administrators with fuzzy medicine”. Chung Hua Hu Li Tsa Chih, 31(7), 395-396.

51. Webb A, Allen R, Smith D, 1996. “Closed-loop control of depth of anaesthesia”. Measurement + Control, 29, 211-215.

52. Westenskow DR, 1997. “Fundamentals of feedback control: PID, fuzzy logic, and neural networks”. J Clin Anesth, 9(6 Suppl), 33S-35S.

53. Wolf M, Keel M, von Siebenthal K, Bucher HU, Geering K, Lehareinger Y, Niederer P, 1996. “Improved monitoring of preterm infants by Fuzzy Logic”. Technol Health Care, 4(2), 193-201.

54. Ying H, Sheppard LC, 1994. “Regulating mean arterial pressure in postsurgical cardiac patients”. A fuzzy logic system to control administration of sodium nitroprusside. IEEE Engineering in Medicine and Biology-Magazine, 13(5), 671-677.

55. Zbinden AM, Feigenwinter P, Petersen-Felix S, Hacisalihzade S, 1995. “Arterial pressure control with isoflurane using fuzzy logic”. Br J Anaesth, 74(1), 66-72.