REGULATION OF HEMODYNAMIC AND ANESTHETIC STATES

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Keywords: Anesthesia, Blood Pressure, Multiple Model Predictive Control, Complexity Analysis

Abstract

Two important monitoring and control topics in critical care are discussed. A multiple-model predictive control approach is used to regulate blood pressure and cardiac output by manipulating the infusion rate of two drugs. Depth of anesthesia is estimated by integrating the complexity, regularity, and spectral entropy information of EEG using an adaptive network based fuzzy inference system (ANFIS). Results based on animal experiments are presented.

1. Background

Anesthesiologists administer anesthetics and monitor the depth of anesthesia (DOA) during surgical procedures. In addition, they may be required to maintain or monitor certain other patient states, such as mean arterial pressure (MAP), by infusing cardiovascular drugs and/or altering the administration of anesthesia. It is known that hemodynamic states such as blood pressure and cardiac output are affected by the anesthetics administered and require close monitoring during surgical procedures. The current clinical practice is to use manual adjustment of anesthetics and drug infusion rates or with "open-loop" programmable pumps. It is desirable to have an automated "closed-loop" system for regulation of hemodynamics states and DOA.

1.1 Hemodynamic Variable Control

Initial research in hemodynamic control focused on single input-single output control of MAP, while more recent work considers the control of several hemodynamic variables by the infusion of multiple drugs. A detailed review of blood pressure control is provided by Isaka and Sebald (1993). Kwok et al. (1997) reported on clinical trials of automated blood pressure regulation during open-heart surgery. There has also been a significant research effort in the simultaneous control of MAP and cardiac output (CO) by manipulating the infusion rate of two drugs (usually sodium nitroprusside and dopamine; Voss et al. 1987, Yu et al. 1992). Our work in developing and implementing model-based control is summarized in section 2.

1.2 Depth of Anesthesia

Inadequate anesthetic levels during surgery can lead to patient awareness with undesirable psychological consequences (Moerman et al., 1993). A monitor capable of estimating depth of anesthesia (DOA) is desirable for assisting the anesthesiologist in minimizing such incidences. However, the significance of the traditional signs of DOA commonly used by the anesthesiologists, such as blood pressure, lacrimation, facial grimacing, movement or diaphoresis have diminished after the introduction of neuromuscular blocking agents as those clinical signs largely depend on the skeletal muscle activity. A more reliable technique independent of the muscular reflexes for measuring the DOA appears to be necessary. A commercially available monitor, the bispectral index (BIS), has been used in a number of monitoring and closed-loop studies. Results have been mixed, and Frenzel et al. (2002) recently recommended that the BIS not be used to infer sedation in a heterogeneous population of surgical care patients. Our work in developing a DOA measure is presented in section 3.

2. Blood Pressure and Cardiac Output

An important issue in the design of drug infusion systems is the need to impose bounds on dosages and infusion rates to avoid overdosing or drug toxicity. Alternatively, the physician may want to specify an operating range of the controlled variables instead of a specific setpoint. A critical challenge is the variability in drug responses, both from patient-to-patient, and during the course of treatment for a single patient. The multiple model predictive control (MMPC) approach that we developed handles constraints and adapts to the dynamic variations in drug responses.

Model Predictive Control (MPC) is a class of control strategies that employ an identifiable model to predict the future behavior of the system over an extended prediction horizon; for a tutorial introduction, see Bequette (2003). An objective function, based on the setpoint tracking error over a prediction horizon, is minimized by adjusting a set of future manipulated variable moves subject to constraints on the manipulated inputs and controlled outputs. The optimization-

based framework of MPC allows computation of the optimal infusion rates subject to input and output constraints.

Any model-based approach relies on the availability and accuracy of the prediction models and requires on-line adaptation to account for patient variability. Our MMPC-based approach uses a bank of several models (first-order + deadtime) to characterize possible dynamic behavior of the patient (Rao et al., 2001). Based on the recent drug responses of the patient, relative weights are assigned to each of the models, to find the best combination of models that describes the behavior. The controller then uses the same weighting of models to predict the future behavior for a hypothetical set of future drug infusion rates. An optimizer finds the best set of future infusion rates, to closely match a desired output trajectory (blood pressure profile, for example). The advantage of our optimization-based approach is that constraints on the drug infusion rates are explicitly enforced. Although a nonlinear constrained optimization approach is used, the control calculations take less than 2 seconds, which is minimal for a system with a sample time of 30 seconds.

The control strategy was first tested on a rigorous simulation of the circulatory system of a dog. The control strategy was then tested in thirteen canine experiments (see Figure 1 for the experimental set-up), involving the use of two anesthetics, isoflurane and halothane. High concentrations of halothane were used to induce conditions of a compromised heart, while isoflurane was used to verify the complexity analysis approach for measuring the depth of anesthesia. The closed-loop response specifications were achieved. Detailed results are presented in Rao et al. (2001, 2003). A review of multiple model-based control approaches, with simulation results, was presented in Schott and Bequette (1997). Aufderheide and Bequette (2003) discuss the many issues associated with a multiple model predictive control formulation.

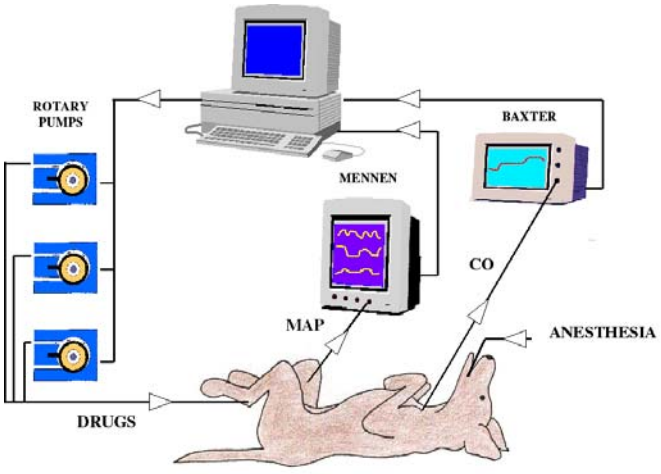

Figure 1. Schematic Diagram of the Experimental Setup (Rao et al., 2001).

Example Single-Output Results. A 19 kg female canine anesthetized with isoflurane was used to study SISO control of blood pressure by manipulating sodium nitroprusside (SNP). Blood pressure is artificially increased by using phenylepherine (PNP). Results using a single model-based controller are shown in Figure 2, while the multiple model-based results are shown in Figure 3. The adaptation ability of the multiple model-based strategy clearly leads to improved performance (a more damped response to setpoint changes).

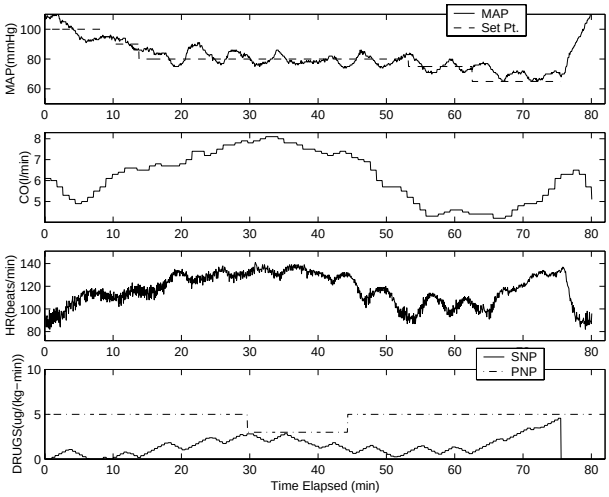

Figure 2. Case 1: SISO control of MAP using SNP in canine under isoflurane; a single model is used for control. PNP is used to induce hypertension.

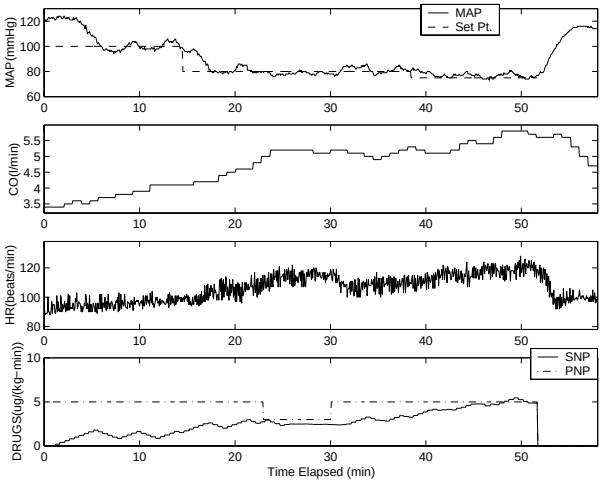

Figure 3. Case 1: SISO control of MAP using SNP in canine under isoflurane; the multiple model approach is used for control. PNP is used to induce hypertension

Example Multivariable Results (Figure 4). For this 20.5 kg female canine, the usual concentration of halothane caused a considerable depression of CO and MAP. The canine's hemodynamic conditions were initially mis-diagnosed and PNP infusion rates had to be raised to 4 µg/(kg dog-min) to induce even reasonable hypertension. When the controller was engaged, the MAP setpoint was lowered to 45 mm Hg and CO desired to be between 3.75 to 5.75 l/min. The high PNP infusion finally took effect around 15 minutes and controller suitably increased SNP infusion rates to lower the MAP. Due to concerns of running SNP at high rates for a long duration, the MAP setpoint was increased progressively during the control run so as to reduce the net SNP infused. The controller was able to maintain the CO in the specified

setpoint band while also maintaining tight control of MAP setpoint. Once again some oscillations in heart rate lead to oscillations in MAP. In this run, we misdiagnosed the canine as phenylephrine finally kicks in and increases baseline MAP too high causing elevated levels of SNP infusion. We raise the MAP set point to limit the total infusion amount of SNP allowing us to have a much longer duration for the experiment. The experiment lasts almost 2.5 hours.

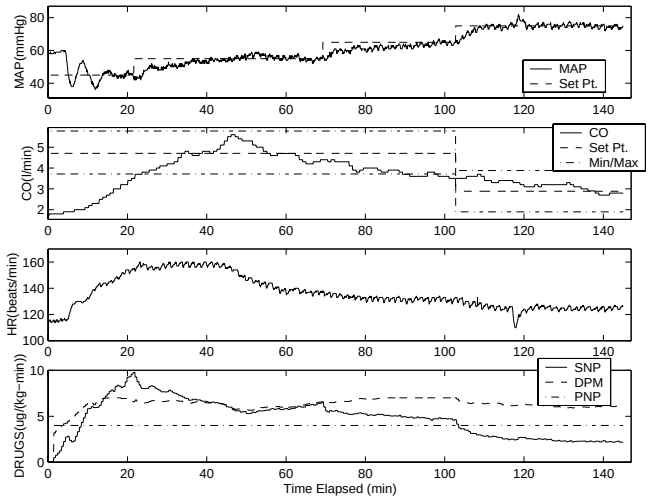

Figure 4. Multivariable control for canine with depressed CO using halothane. Dopamine (DPM) and sodium nitroprusside (SNP) are controlled inputs. PNP is used to induce hypertension.

Since the current state of the art is manual regulation, we compared the automated closed-loop performance with that of manual control. The multiple model predictive controller maintained MAP within $\pm$ 5 mm Hg 88.9% of the time with a standard deviation of 3.9 mm Hg. The cardiac output was held within $\pm$ 1 liter/min 96.1% of the time, with a standard deviation of 0.5 liters/min. The manual runs maintained MAP only 82.3% of the time with a standard deviation of 5 mm Hg, and cardiac output 92.2% of the time with a standard deviation of 0.6 liters/min. It should be noted that the performance of manual control in practice is expected to be much lower than these experiments, since an anesthesiologist would be dividing her efforts among numerous activities; in these experiments we were devoted solely to regulating MAP and CO. In any event, the automated system performance is better than manual control, and frees up the anesthesiologist to monitor other difficult to measure variables.

3. Anesthetic Depth

Currently there is no reliable means of assessing the depth of anesthesia (DOA) of a patient during surgery. An anesthesiologist controls the level of anesthetic titration based on observable measurements of state variables such as hemodynamics, and other signs of DOA. The decision-making process that ultimately leads to changes in the anesthetic titration level is a complex process that very much relies on the experience and knowledge of the anesthesiologist in interpreting those state variables. A fuzzy logic system can thus be substituted for the operation of anesthesia management where the anesthesiologist's knowledge is transcribed and modeled as fuzzy rules for the task of state variable transformation into estimation and controlling actions. The flow of such fuzzy estimation and control process is illustrated in Figure 5.

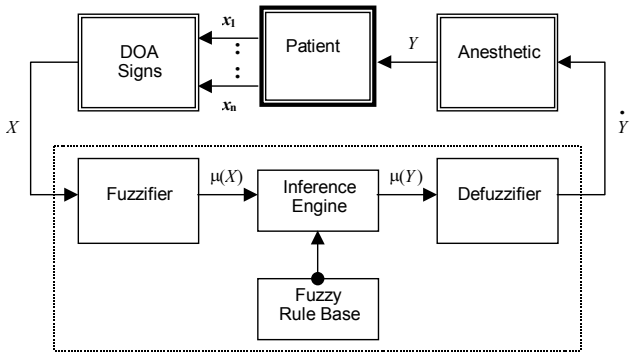

Figure 5. Basic architecture of a fuzzy logic controller based on some physician knowledge model. The DOA signs may be any of the "traditional observable inputs" such as hemodynamics, body temperature, patterns of spontaneous breathing, and other indications of awareness. The fuzzy rule base stores the empirical knowledge of the anesthesiologists relating anesthetic titration requirements to changes in DOA signs.

The *x's* are the signs of DOA measured or secondarily computed, obtained via the sensors placed on the patient. An input variable of the *x's* can be any of the current state (arterial blood pressure), state error (change in arterial blood pressure), state error derivative (rate of change in arterial blood pressure), and state error integral. The output of the fuzzy controller changes the current level of anesthetic titration as necessary based on the fuzzy inference process relating the *x's* to that of the anesthetic needs. This process emulates the thought processes of an anesthesiologist in determining the need for changing the titration level based on a collection of observable parameters.

This fuzzy logic model is based on the states and the changes of various indirect indicators of the DOA, which are variant in a nonlinear system and constantly influenced by unpredictable external events Infusions of vasoactive and inotropic drugs diminish the correlations between anesthetic dosage and hemodynamic variability. Furthermore, surgical events and external disturbances reduce the significances of other indirect indicators of the DOA such as breathing patterns and bodily temperatures. We have examined the electroencephalogram (EEG) to see if it may be an effective sign of the DOA associated with an increasing concentration of anesthetics (Jang, 1993).

Neuro-Fuzzy Modeling

Adaptive network based fuzzy inference system (ANFIS), as a neuro-fuzzy method, combines fuzzy logic and neural-nets into a five-layer adaptive network architecture. Details about the structure and learning procedure of ANFIS are in Jang (1993).

To build a derived fuzzy knowledge model based on ANFIS for estimating DOA, two types of tuning (i.e. model structure tuning and parameter tuning) are required. Structure tuning concerns the structure of the rules: input and output variables selection, variable universe of discourse partition, linguistic labels determination, and type of logical operation to compose each rule. Parameter tuning mainly concerns the fine adjustment of the position of all membership functions together with their shape controlled by *premise parameters* and the Takagi-Sugeno type (Sugeno and Kang, 1988) if-then rules to be extracted controlled by the *consequent parameters*.

ANFIS employs an efficient hybrid learning procedure that combines gradient descent method and the least squares estimation to tune the parameters both of the membership functions and the Takagi-Sugeno type rules. Each epoch of the learning procedure is composed of a forward pass and a backward pass. In the forward pass, the input data and functional signals go forward to calculate each node output while the premise parameters are fixed, and the consequent parameters are optimized via least-squares estimation. After the optimum consequent parameters are found, the functional signals keep going forward until the output of the network is calculated and the error measure is estimated. Then the backward pass starts. In this stage, the output error propagates from the output end toward the input end while consequent parameters are fixed, and the premise parameters are optimally updated by the gradient method via a standard back-propagation algorithm. Not only can this hybrid learning procedure decrease the dimension of the search space in the gradient method, but, in general, it will also cut down substantially the convergence time. The least-squares method is, actually, the major driving force that leads to fast training. As a result, ANFIS can usually generate satisfactory results right after the first epoch of training**,** that is, after the first application of the least-squares method. Since the least-squares method is computationally efficient, it can be used for on-line application.

Before training, the *consequent parameters* of the ANFIS are all set to zero. As a conventional way of setting parameters in a fuzzy system, the *premise parameters* are set in a way that the membership function can cover the universe of discourse completely, with sufficient overlapping.

Neuro-Fuzzy Based CI Model for EEG

The nonlinear nature of brain neuronal activity contributes to the formation of the EEG with very complex dynamics (Koch and Laurent, 1999; Micheloyannis et al., 1998). Moreover, the EEG may not be simply generated by a purely deterministic or stochastic process, but rather by some combination of both. The EEG does not change in a linear or monotonic fashion with changes in DOA, and different EEG-derived parameters are not equally useful in estimating DOA. The derived parameters should be used in combination and each method weighted differently as the EEG changes nonlinearly with various levels of stimulation and from light to deep anesthesia. The emerging computational intelligence, neuro-fuzzy method, can act as a promising modeling candidate. By nonlinear quantitative analysis two EEG-derived parameters, complexity measure *C(n)* (Kaspar, F. and Schuster, 1987) and approximate entropy *ApEn* (Pincus et al., 1991), are extracted from the raw EEG signals and merged together with the spectral entropy *SE* (Rezek and Roberts, 1998) for estimating DOA. *C(n)* and *ApEn* quantify the complexity and regularity of the EEG dynamic patterns in a manner consistent with our intuition, as well as being model-independent statistics.

Complexity Analysis

Complexity is a common characteristic of many phenomena, especially for biological systems, with the brain often described as the most complex biological system (Koch and Laurent, 1999). Its electrical activity (EEG) exhibits significant complex behavior, which is generated by numerous neuroelectrical events within the brain's structure. The complexity measure $C(n)$, proposed by Lempel and Ziv (1976), is extremely well suited for characterizing different spatiotemporal patterns with chaotic temporal components and their development in high-dimensionality nonlinear systems. Compared with other types of complexity measures, the computation of $C(n)$ is simpler, faster, and more suited to real-time EEG analysis (Zhang and Roy, 1999). Complexity measures the number of distinct patterns that must be copied to reproduce a given string. The only computer operations considered in constructing a string are copying old patterns and inserting new ones. Briefly described, a string $S=s_1s_2\ldots s_n$ is scanned from left to right, and a complexity counter $c(n)$ is increased by one unit every time a new sub-string of consecutive characters is encountered in the scanning process. After normalization, the complexity measure $C(n)$ reflects the rate of new patterns arising with the increase of string length n. Detailed algorithms for $C(n)$ can be found in Kaspar and Schuster (1987) and Lempel and Ziv (1976).

Regularity Analysis

Approximate Entropy (*ApEn*) is developed to quantify the amount of regularity in the data without any *a priori* knowledge about the system generating them (Pincus et al., 1991). It is a nonnegative number that will distinguish among data sets, with larger numbers indicating more irregularity, unpredictability, and randomness. *ApEn* is nearly unaffected by low level noise, is robust to occasional very large or small artifacts, gives meaningful information with a reasonable number of data points, and is finite for both stochastic and deterministic processes. These features are useful for quantitatively characterizing changes in the evolving regularity of the EEG. While applying *ApEn* to the EEG, a particular model form is not being sought, such as deterministic chaos, but the intent is to distinguish among the EEG data sets collected under different anesthesia conditions on the basis of regularity. Such regularity can be seen in both deterministic and/or random (stochastic) processes, similar to brain activity. Detailed algorithms for *ApEn* can be found in (Pincus et al., 1991).

Spectral Entropy Analysis

Spectral entropy (*SE*) (Rezek and Roberts, 1998) is selected as the third derived parameter. This measure quantifies the spectral complexity of the EEG signal. The power spectral density (PSD) $\hat{P}(f)$ can be obtained from the EEG signal by a fast Fourier transformation (FFT). The normalization of $\hat{P}(f)$, with respect to the total spectral power, will yield a normalized density function. Application of Shannon's channel entropy gives an estimation of the spectral entropy (*SE*) of the underlying EEG process, where entropy is given as

$$H = \sum_f p_f \ln(1/p_f) \qquad (1)$$

p_f is the normalized density function value at frequency *f*. Heuristically, the entropy has been interpreted as a measure of uncertainty about the event at *f*.

ANFIS - "Derived" Fuzzy Knowledge Model

By using the ANFIS method, fuzzy if-then rules are obtained to express the complex relationship between the three derived parameters and anesthesia states. These rules are then used to construct a derived fuzzy knowledge model for providing a single variable to represent the DOA. The meaning of the word "derived" is triple-fold: (1) the input parameters are derived from the EEG by signal processing, not like the hemodynamic parameters, heart rate and blood pressure. (2) the fuzzy knowledge is derived with the help of ANFIS, not directly from experts. (3) the final model and the *DOA* index are derived, not from published data or experience.

System Design Based on ANFIS for EEG

The designed DOA estimation system (Figure 6) consists of two paths: a dashed line path for off-line training of the ANFIS before the system put into operation and a solid one for on-line DOA estimation. These two parts contain similar function blocks: EEG collection, Parameters Extraction, and ANFIS. Before the system goes into operation, a Specific Raw EEG Database must be first built for off-line training of the ANFIS. The complexity *C(n)*, regularity *ApEn*, and spectral entropy *SE* are extracted from the raw EEG and form an input feature vector for training the ANFIS. After training, the derived fuzzy if-then rules can be used for on-line DOA estimation. During the on-line application, the recorded EEG is also stored in the Specific Raw EEG Database for updating. Thus, every certain period (Δt) the ANFIS is retrained using the newly updated Specific Raw EEG Database and then the new *premise* and *consequent* parameters are sent to the Trained ANFIS for updating its fuzzy if-then rules. In so doing, the system is dynamic not static, and can be continuously refreshed. In addition, a Specific Raw EEG Database for different anesthetic regimens can be constructed. Thus, regimen-specific or general-purpose DOA estimation systems can be easily built.

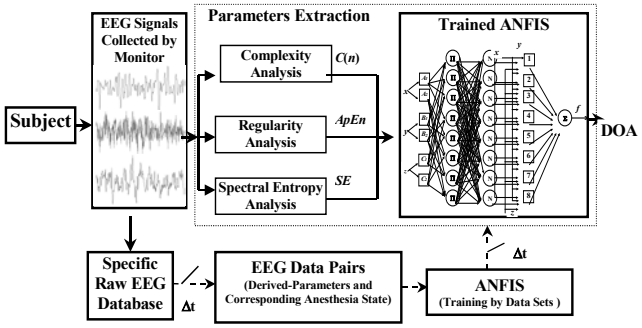

Figure 6. The system diagram for estimating DOA during anesthesia by integrating the complexity, regularity, and spectral entropy information of EEG via ANFIS: dashed flow line for off-line training ANFIS and solid flow line for on-line estimating DOA. Δt denotes that every certain period (Δt) the ANFIS are retrained using the updated Specific Raw EEG Database. The "derived" fuzzy knowledge model is encircled by the dotted rectangle.

ANFIS System: Experiment Results

Thirty experiments using 15 dogs undergoing anesthesia with three different anesthetic regimens (propofol, isoflurane, and halothane) were performed and a database was obtained. The database consists of EEG recordings and the associated, clinically derived anesthesia states. Totally, 134 EEG recordings were obtained from the propofol experiments, 109 recordings from isoflurane experiments, and 64 recordings from halothane experiments. To verify and justify the performance of the model in discriminating awake and asleep states and test the applicability for practical use of the model under different anesthetic regimens, the EEG data sets collected under a specific regimen were used to train and test the model. The test results are listed in Table 1.

Table 1. Test results by the derived fuzzy knowledge model using the "leave-one-out" procedure for three kinds of regimens, respectively (*i.e.* training and test data sets from the same kind of regimen).

Anesthetic Regimen	***State***	Sensitiviy **(%)**	**S**pecificity **(%)**	Accuracy **(%)**
Propofol	Awake	92.3	88.4	90.3
	Asleep	88.4	92.3	90.3
Isoflurane	Awake	89.6	95.1	92.7
	Asleep	95.1	89.6	92.7
Halothane	Awake	82.1	94.4	89.1
	Asleep	94.4	82.1	89.1

The ANFIS is a useful tool in eliciting knowledge from the training input-output data pairs for building the DOA model. The derived numerical quantitative features from EEG by signal processing, such as C(n), ApEn, and SE, contain the relevant information about the DOA, but the anesthesiologists have no direct knowledge and expertise using them for assessing DOA. After training ANFIS, the information derived as fuzzy rules are used here as a framework for knowledge representation. The final output of the model is just one single DOA number between 0.0 and

1.0. The number 0.0 represents full awake and 1.0 denotes a flat line of EEG, or complete EEG suppression.

Discussion

Table 1 shows that the neuro-fuzzy based model has an accuracy in the range of 90% for detecting awake and asleep states under different specific anesthetic regimen. This also demonstrates the capability of the *DOA* index in quantitatively characterizing the level of anesthesia is clinically acceptable. The DOA number correlates well with the level of anesthesia. Moreover, the DOA number is subject independent (i.e. not sensitive to the large intra- and inter-individual variability), therefore, calibration will not be necessary for any specific individual to be monitored. The output of the proposed model offers all the desirable features for a DOA monitoring index, therefore, this makes the proposed fuzzy knowledge model a promising candidate as an effective tool for continuous assessment of the depth of anesthesia.

4. Summary and Future Work

Mean arterial pressure and cardiac output are regulated using a multiple-model predictive control approach. This strategy adapts to handle varying inter- and intra-patient dynamics using a Bayesian weighting function. Constraints on manipulated and controlled inputs are handled using the optimization-based technique. Depth of anesthesia is estimated by integrating the complexity, regularity, and spectral entropy information of EEG using an adaptive network based fuzzy inference system (ANFIS). Results are verified in animal experiments.

Future work includes integrating hemodynamic variable control with the direct control of DOA by manipulating the anesthetic delivery rate. While a multiple-model predictive control strategy readily handles many of the challenges imposed drug and anesthesia delivery, practical implementation in an operating room environment requires the development of a user-friendly interface that does not require knowledge of control theory. For example, to vary the speed of response it would be desirable to use simple faster/slower buttons.

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