國 立 交 通 大 學

生醫工程研究所

碩 士 論 文

麻醉給藥輔助評估系統之開發

The Development of an Assistant System in Drug

Administration of Anesthesia

研 究 生：許懷元

指導教授：蕭子健　教授

中 華 民 國　九 十 八 年 十 月

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麻醉給藥量輔助評估系統之開發

研 究 生：許懷元　　　　　　　　　　　　　　　　　指導教授：蕭子健

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摘要

本論文的目的在於開發並設計一麻醉給藥量輔助評估系統，其角色就如同一虛擬麻醉科醫師，在麻醉的給藥量調控過程中給予麻醉執行者建議，並期望能將麻醉深度維持在適合的深度。

在方法上，利用類神經模糊網路學習能力及模糊推論系統的類人類推論方式，希望能夠使系統具備麻醉科醫師調控給藥量的經驗及智慧。在實驗的設計上，採用麻醉模擬器作為實驗執行之環境，希望充分利用模擬器的優勢，在測試系統上能夠達到理想的效果。實驗分為兩階段進行，結果顯示系統具備初步之能力。

The Development of an Assistant System in Drug Administration of Anesthesia

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Abstract

The main purpose of this thesis is to develop an assistant system in the drug administration of anesthesia. The character of the system is like a virtual anesthesiologist. It gives advices to the anesthesia practitioner on drug administration during the procedure of anesthesia. The expectation is to maintain the anesthesia in the proper depth.

Utilize the learning and the human-like reasoning ability of the fuzzy neural network. We designed the virtual anesthesiologist to accommodate the knowledge and the experience of the real anesthesiologist in anesthetic drug administration. We adopt the anesthesia simulator into the experiment environment to test the virtual anesthesiologist and to explore the value of the simulator. The experiment is divided into two different phases. The results reveal the preliminary capability of the virtual anesthesiologist.

Acknowledgement

First of all, I would like to express my grateful appreciation to my advisor, Dr. TC Hsiao, for his great patience, guidance, supervision, and help advice throughout my Master degree. Your advices helped me when I encountered difficulties in my research. And also thanks for Dr. Wu, without his professional aid in anesthesia and kindly advices, there is no way I can finish the thesis. Professor CY Wang, professor CT Lin, professor JH Lin, and professor YJ Hu, thanks for your kindly advice for me and for the thesis.

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Content

List of Figures

List of Tables

Chapter 1. Introduction

1.1. Motivation

The purpose of the anesthesia is to maintain a steady state for specific operations in clinic. In general, one anesthesiologist utilizes anesthetic drugs and anesthetic skills to make sure that patient will not feel any pain during surgical procedure. In other clinical words, anesthesiologist restrains the stimulations of pain toward patient psychologically and physiologically in order to facilitate the surgical operation.

Anesthesia is a complicated scientific procedure. The similarities of aviation and anesthesia have been discussed in the aspect of educational environment [1] and automation [2]. The maintenances of anesthesia and flight require the observation of monitoring devices of aircraft and the signs of patient. The decision making is in a dynamic and complex environment. Critical accidents are rare but once it happened, the correctness has to rely on the pilot or the anesthesiologist. There are many automatic aviation programs or the autopilot system in the aviation field, such as the aircraft flight control [3] and the unmanned air vehicles [4]. Even though there are some automations or assistant systems in the fields of medicine, for example using PYXIS® for medication and supply management (CareFusion, San Diego, US), InfusO.R. Syringe Pump for administration aid of intravenous agents given during anesthetic procedures (Baxter, Deerfield, US), medical automation to reduce the burden of health care [5], and airway pressure controller for treatment of obstructive sleep apnea [6]. The automatic assistants of making decision from anesthesiologist during surgical operation are still limited to develop. The performance of the procedure is still mostly depended on authorized anesthesiologist's experience.

From side view of computer science development, the automatic assistants are achieved through the specific background knowledge, information processing ability, and powerful system integration. The information-based and knowledge-driven assistant is worth to be investigated and to be applied on anesthesia procedure. As studying on Institute of Biomedical Engineering, College of Computer Science here, is it possible to facilitate the making decision procedure from anesthesiologist and/or reduce the surgical operation loading during sedation? It is a great and deep motivation to become the original purpose of this research.

1.2. Literature study

One of clinical anesthetic loadings or sedation procedure is to restrain specific physical and mental responses of the patient stimulated by the surgical operations. It is complex to be treated as an art of removing all sensations, whether it is the sense of pain, touch, temperature, or position [7]. Becoming a qualified anesthesiologist, in general, one must receive a medical degree from an accredited medical school, take an additional three or four-year residency training about anesthesiology in medical center, and pass qualified exams from Board Certification Committee of Society of Anesthesiologists. The task of the anesthesiologist is to control the patient in the continuum between consciousness and unconsciousness, pain and analgesia, muscle activity and relaxation [8]. Anesthesiologist carefully maintains the depth of anesthesia (DOA) in proper levels for different surgical operations. Inadequate levels of anesthesia may cause unfavorable psychological and/or physiological consequences, for example inter-operative awareness, anesthetic drug underdosing, and overdosing [9-11].

One anesthesiologist often makes decisions on maintaining the DOA by training procedure and their own experiences. Anesthesiologists adjust the anesthetic heuristic by observing meaningful changes in vital signs, i.e. heart rate (HR**)**, blood pressure, muscular movement, and breathing status. During the past decades, several method and designs have been developed to judge the concentration of drug induction [12-13], and the definition of DOA. For example, Tackley designs a computer controlled infusion pump to deliver propofol to patients undergoing body surface surgery [14] Robb used systolic arterial pressure to automatically adjust the dose of enflurane for routine major gynaecological surgery [15], Toshinori constructed a closed-loop blood pressure control system using fuzzy logic during enflurane anesthesia for a variety of surgeries with cerebral, cardiac, or other vital organ dysfunction [16], Schwilden examined the applicability of a closed-loop feedback control of propofol anesthesia by quantitative electroencephalogram (EEG) analysis for 11 volunteers [17], and Elkfafi described a self-organizing fuzzy logic model for auditory response monitoring and control of DOA off-line analysis during body surface or abdominal surgery [18].From Zadeh proposed the concepts of fuzzy at 1965 [19], the theory of fuzzy logic and application of fuzzy system have been widely used in many fields, such as pattern recognition [20], aircraft control [21], internet security [22], and medical application [23]. Asbury and Tzabar wrote an editorial for British Journal of Anaesthesia in 1995 and concluded that the use of fuzzy logic control became the way to model real world imprecision and complexity of anaesthesia [5]. It considered that fuzzy logic can imitate the anesthesiologist cognitive processes. After that, fuzzy logic has been wildly applied in anesthesia and has been shown to mimic the human experts. For example, Huang provided the continuous propofol sedation for head injury, unconsciousness, and mechanical ventilation in neurosurgical intensive care unit. The results indicate that fuzzy logic controller can easily mimic the rule-base of neurosurgeons to achieve stable sedation [24]. Hooper designed a two-stage fuzzy logic system to clinical anesthesia demonstrated that the oxygen supplement decision support system during Low-flow/ closed-loop anesthesia with expert knowledge of an anesthetist [25].

Fuzzy logic allows membership degrees to variables and use linguistic terms, making it close to human thinking style. Fuzzy system evaluates results according to if-then rules. The expert experience for the construction and tuning of the fuzzy system plays an important role in obtain the optimum results. Sometimes the expert experience is not directly available, neuro-fuzzy methods are discovered to help the development, the refinement of the expert knowledge or the experience [26]. For example the Fuzzy Adaptive Learning Control Network (FALCON) [27], Adaptive Network-based Fuzzy Inference System (ANFIS) [28], and the adaptive Fuzzy Neural Networks (FuNN) [29]. Different neuro-fuzzy networks are with different structures and learning algorithms. The different between traditional fuzzy systems and the neuro-fuzzy networks are the learning ability of the neuro-fuzzy networks. It can facilitate the building in the membership functions and the if-then rules of the fuzzy system. Recently there are several applications of neuro-fuzzy networks in the field of anesthesia. Zhang and Roy used the ANFIS with EEG-derived parameters to estimate the DOA [26]. Yardimci used ANFIS and cardiovascular parameters the blood pressure, and the **HR** to control the DOA [30].

1.3. Objective

The objective of this research is to adopt the intelligence theory of computer science into the development of the assistant system in anesthetic drug administration. The goal of this assistant system is to provide adequate drug administration advice during the anesthesia procedure and to accommodate the knowledge of the anesthesiologist in drug administration.

Chapter 2. Methods and materials

2.1. Fuzzy Theory

Fuzzy set theory was first proposed by Zadeh in 1965. It quantifies the uncertainty of the human thoughts. The transform of the uncertainty and the evaluation procedure are mainly based on the degree of membership. The concept of the degree of membership let fuzzy theory is favorable in dealing with the problem which has the characteristic of ambiguous and unspecific. In the following section the introduction of fuzzy theory will focus on membership function, basic fuzzy set operations, and the fuzzy inference system.

2.1.1. Membership function

The distinction between the traditional set theory and the fuzzy set theory is that the boundary of classical set (or crisp set) is rigid and sharp, and the boundary of the fuzzy set is blurred or vague. The distinction can be shown by the definition of membership function.

$$A = \{(x, u_A(x)) \mid x \in U, 0 \le u_A(x) \le 1\} \tag{2-1}$$

A fuzzy set A can be defined as formula (2-1). U is the universe of discourse, and $\mu_A(.)$ is the membership function. Membership function defined the degree

(degree of membership) that one element is belong to a fuzzy set, for example $\mu_A(x)$, and $\mu_A(x)$ can be defined as formula (2-2). The shape of this function is like Fig. 2.1, the bell shape.

$$\mu_A(X) = \exp\left[-\frac{(x-c)^2}{2\sigma^2}\right] \quad (2\text{-}2)$$

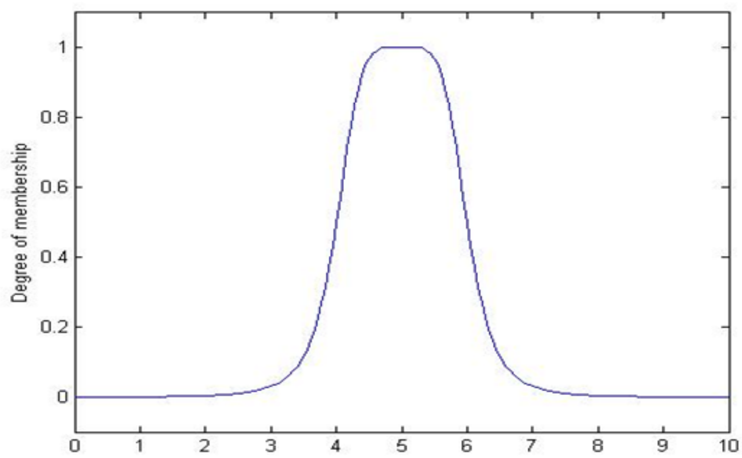

Fig. 2.1 Gaussian bell shape function

For an classical set A', the membership function can be defined as formula (2-3), and the shape of this membership function can be seen in Fig. 2.2 it content a very sharp boundary.

$$\mu_A'(X) = \{\begin{matrix} 1, x \in A' \\ 0, x \notin A' \end{matrix} \quad (2\text{-}3)$$

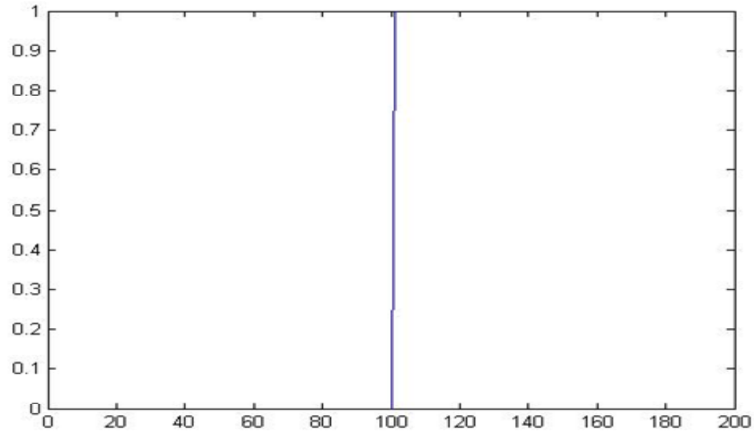

Fig. 2.2 The shape of crisp set membership function

2.1.2. Fuzzy set operations

Basic and standard operations of fuzzy sets were introduced from Zadeh in 1978 [Fuzzy sets as a basis for a theory of possibility,]. We used some basic and standard operations to construct design fuzzy system, i.e. intersection, union, complement, equality, and subset. If the $\mu_A(x)$ and $\mu_B(x)$ are the membership functions of fuzzy sets A and B respectively, the definitions of above operations are as shown as follows,

1. Intersection: the intersection of fuzzy sets A and B is denoted as $A \cap B$,

$$\mu_{A \cap B}(X) \equiv \min\left[\mu_A(X), \mu_B(X)\right] \equiv \mu_A(X) \wedge \mu_B(X), \forall x \in U \tag{2-4}$$

where $\wedge$ is the min operation.

2. Union: the union of fuzzy sets A and B is denoted as $A \cup B$,

$$\mu_{A \cup B}(X) \equiv \max\left[\mu_A(X), \mu_B(X)\right] \equiv \mu_A(X) \vee \mu_B(X), \forall x \in U \tag{2-5}$$

where $\vee$ is the max operation.

3. Complement: the complement of fuzzy set A is defined as $\mu_A(X) \in [0,1]$,

$$\mu_{\bar{A}}(X) \equiv 1 - \mu_A(X), \forall x \in U \qquad (2\text{-}6)$$

the $\mu_{\bar{A}}(x)$ is the membership function of $\bar{A}$.

4. Equality: the complement of fuzzy sets *A* and *B* are equal if and only if

$$\mu_A(X) \equiv \mu_B(X), \forall x \in U \qquad (2\text{-}7)$$

5. Subset: the subset A of fuzzy set B is denoted as A $\in$ B if and only if

$$\mu_A(X) \le \mu_B(X), \forall x \in U \qquad (2\text{-}8)$$

2.1.3. Fuzzy inference system

Fuzzy inference is derived from fuzzy set theory, and based on fuzzy IF-THEN rules and fuzzy inference. The structure of one fuzzy inference system include: fuzzifier, fuzzy (IF-THEN) rule base, inference engine, and the defuzzifier. The structure of the fuzzy inference system is shown in Fig. 2.3 and each component is explained in the following section.

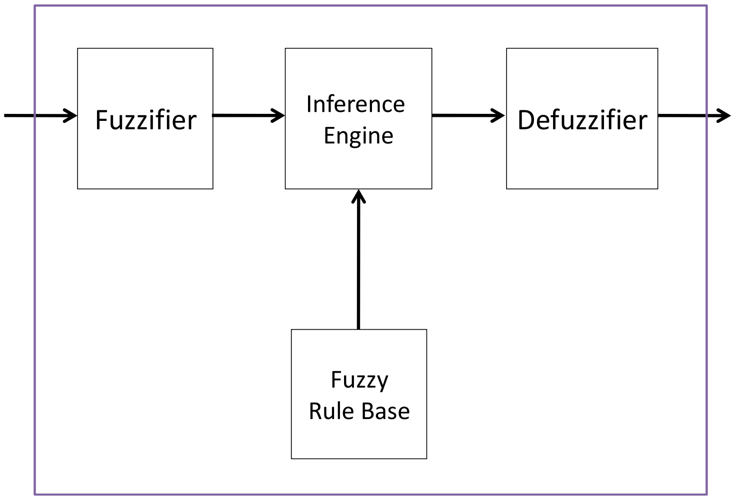

Fig. 2.3 Structure and component of fuzzy inference system

1. **Fuzzifier:** fuzzifier utilizes membership function to map the real word value into the fuzzy set. The main purpose is to let mostly the exact value we measured or detected (for example, the **HR** of the patient) could be transformed into the value that can be process by the inference engine with the fuzzy IF-THEN rules.
2. **Fuzzy Rule Base:** fuzzy rule base is composed by a group of IF-THEN rules. These rules characterize the relations between the input and output of the system. Rules can be gathered either by the expert experience or by analysis the real data.
3. **Inference engine:** inference engine is the core of the system. It processes the input fuzzy sets and get fuzzy output sets. The output fuzzy set is evaluated base on the fuzzy IF-THEN rule. There are three types of fuzzy inference that is most commonly used, Mamdani fuzzy inference, Sugeno fuzzy inference, and the Tsukamoto fuzzy inference. The way of operation of Sugeno type fuzzy inference mode can be seen in Fig. 2.4
4. **Defuzzifier:** the purpose of the defuzzifier is opposite to the fuzzifier. It transforms the value of fuzzy sets into the exact value that is meaningful and can be used in the real world. The methods that are mostly commonly used are: center of area, center of sums, height, and first of maximum.

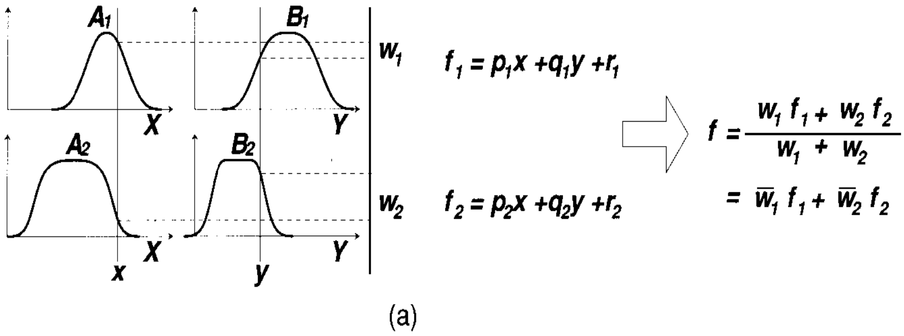

Fig. 2.4 Sugeno type fuzzy inference [28]

2.2. Fuzzy neural networks and ANFIS

2.2.1. Fuzzy neural networks

Fuzzy theory has been widely used in different areas. Based on fuzzy theory and IF-THEN rules, fuzzy inference system can easily mimic the thoughts and the reasoning procedure of human being. That makes it having the ability to combine the human expert knowledge. Meanwhile the artificial network has excellent learning ability. Therefore, neuro-fuzzy networks which combine the advantages of these two kinds of structure have been proposed. It based on the fuzzy inference system and has the learning ability of artificial neural network and can avoid the limitation of the traditional fuzzy inference system. Which is, the tuning and refinement of the system (rules and membership functions) has to be rely on the knowledge of human (trial and error method). There are three typical kinds of neuro-fuzzy network structure which are most commonly used: fuzzy adaptive learning control network (FALCON) [27], adaptive network-based fuzzy inference system (ANFIS) [28], and backpropagation fuzzy system. In the next section we will introduce the ANFIS structure.

2.2.2. Adaptive network-based fuzzy inference system (ANFIS)

Adaptive network-based fuzzy inference system is proposed by Jang in 1993 [28]. It is based on the fuzzy inference system and integrated into the hybrid learning procedure. By means of the hybrid learning procedure, it can tuning the refine itself and gradually adjusts out the proper membership function to fit the relationship between input and output. The structure of ANFIS can be seen in Fig. 2.5

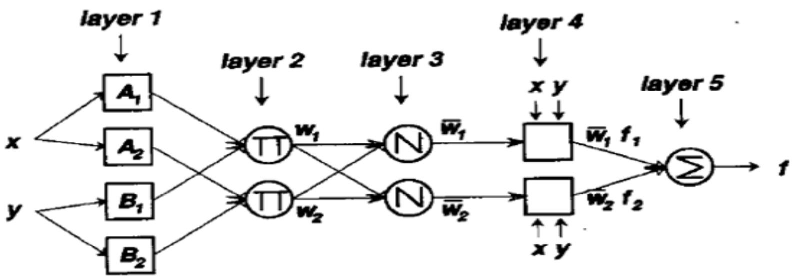

Fig. 2.5 Structure of ANFIS [28]

1. **Structure:** as shown in Fig. 2.5, there are five layers in a typical ANFIS structure. Each neuron in the same layer with same operation, and can be compared with the inference procedure of fuzzy inference system. For the simplification reason, we assume there are only two input and one output in the structure and each layer has been described in the following of this sector.

   Layer 1 (input layer):
   The function of layer one is to map the input variable into the relative fuzzy sets. By means of the membership function, we can transform the exact value of input variable into the degree of membership. As shown in Fig. 2.5, each square is a membership function. There are several kinds of membership, in this research just like most cases, the bell-shaped

membership function has been chosen (2-9). Parameters in this layer are referred to as premise parameters.

$$\mu_A(X) = \exp\left[-\frac{(x-c)^2}{2\sigma^2}\right] \tag{2-9}$$

Layer 2 (fuzzy inference and rule base layer):

Neurons in this layer are labeled as II. It carries out T-norm operation, and the output of each node represents the firing strength of a rule. One example of this operation is (2-10).

$$w_i = \mu_{A_i}(x) \times \mu_{B_i}(y),\ i = 1,2 \tag{2-10}$$

Layer 3 (normalize layer):

This layer normalizes the output from the previous layer. The operation has been shown in (2-11)

$$\overline{w_i} = \frac{w_i}{w_1 + w_2}, i = 1,2 \tag{2-11}$$

Layer 4 (defuzzifier layer):

The operation of this layer is shown in (2-12), each node i with the same function

$$O_i^4 = \overline{w}(p_i x + q_i y + r_i) \tag{2-12}$$

where w_i is the output of layer three. The parameters of this layer (p_i , q_i , and r_i) is referred to as consequent parameters.

Layer 5 (output layer):

There is only one node in this layer (as shown in Fig. 2.5). It is labeled as $\sum$, and the output of this layer is the summation of the incoming signal (the outputs of the previous layer).

$$o_1^5 = \sum_i \overline{w_i} f_i \tag{2-13}$$

2. **Learning Procedure:** the parameters in ANFIS can be divided into the premise parameters (2-8) and consequent parameters (2-11). Premise parameters are nonlinear parameters, while the consequent parameters are the linear parameters. Jang proposed hybrid learning procedure, and using least square estimator to adjust linear parameter set while using the steepest descent method to adjust the nonlinear parameter set.

2.3. Bispectral index (BIS)

Intraoperative awareness often leads to psychological and physiological damages. A method or a device which is capable of estimating or measuring the DOA is desirable and helpful for assisting the anesthesiologists in minimizing the occurrence of such accidents. The EEG signals is generated from the central nervous system and can be treated as a sign of DOA because of the graded change in frequency domain associated with an increasing concentration change in anesthetics [31]. Features which are processed from the raw EEG have been proposed and can be correlated with DOA. For example the 95% spectral edge frequency [32], the median frequency [33], and the value of Bispectral index (**BIS**) [32].

The calculated value of **BIS** is based on the correlation between the phases of the different wave components of the EEG which is a weighted sum of EEG sub-parameters including a time domain, a frequency domain, and higher order spectral information. The value range of the **BIS** is normalized into 0~100. **BIS** 0 and **BIS** 100 reflect no EEG activity and totally awake state, respectively. In surgical circumstance, **BIS** 40 and 60 are used as the adequate level for general anesthesia. In 1996, the US Food and Drug Administration (FDA) had been approved that BIS monitoring was used for assessing the hypnotic effects of general anesthetics and sedatives. In 2003, FDA had been also approved that **BIS** was a parameter to control awareness incidence in surgery.

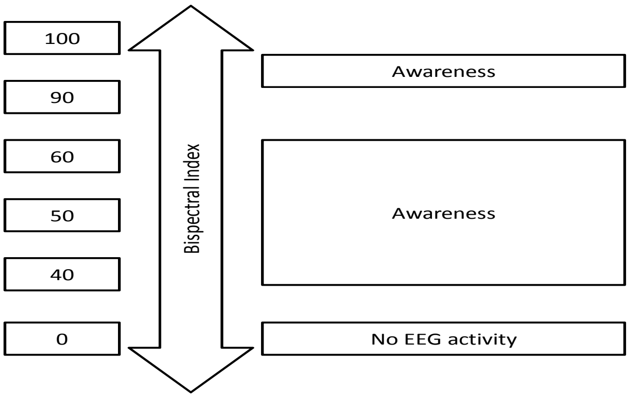

Fig. 2.6 Bispectral Index

2.4. Propofol

Propofol is a drug that eases or controls anxiety and tension, and encourage relaxation and sleep or loss of consciousness. It is an intravenously administered hypnotic agent, and with the short acting characteristic. It has been used mostly in induction and maintenance of general anesthesia, sedation for mechanically ventilated adults, and procedural sedation. There is no report or research have shown that propofol will cause **HR** significantly change. Propofol has been proved by investigation that it tackles well in control problem for hypnosis [34-35]. The chemical structure of propofol is shown in Fig. 2.7. The property of propofol is shown in Table 2.1

.

Table 2.1 Information of Propofol

	Propofol
Onset(min)	1-2.5
Clinical Duration (min)	15-30
Amnesia	Incomplete
Analgesia	No
Safety (therapeutic)	Narrow

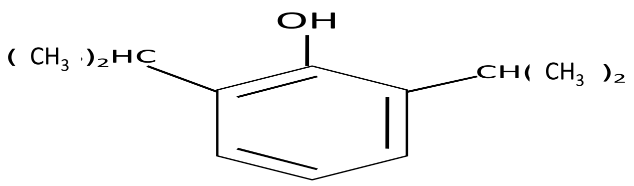

Fig. 2.7 Chemical structure of propofol ($C_{12}H_{18}O$)

2.5. Anesthesia simulator

Anesthesia simulator has been more and more popular these days. There are several applications of anesthesia simulator: for training, for assessment of clinical competence, for studying of anesthesiologist's behavior, and for the design and evaluation of new anesthesia equipment [36]. There are two kinds of anesthesia simulator, the high fidelity and the low fidelity. High fidelity simulator using a mannequin, real anesthesia machines, monitors and equipments can mostly recreate the anesthesiologist working environment, while the low fidelity anesthesia simulator utilizing computer screen to accommodate these information. In these researches we choose MEDIQ Anesthesia Simulator, which is a low fidelity simulator manufacturing by MEDIQ Abraxas AB in Sweden. It is for theoretical anesthesia training and has been used as a teaching aid in several university teaching hospitals in Sweden. The simulator provides several different surgical and patient-characteristic setting. It is noteworthy that the simulator adds some random events or disturbances to make the cases with slightly differences even with the same surgical and patient-characteristic setting.

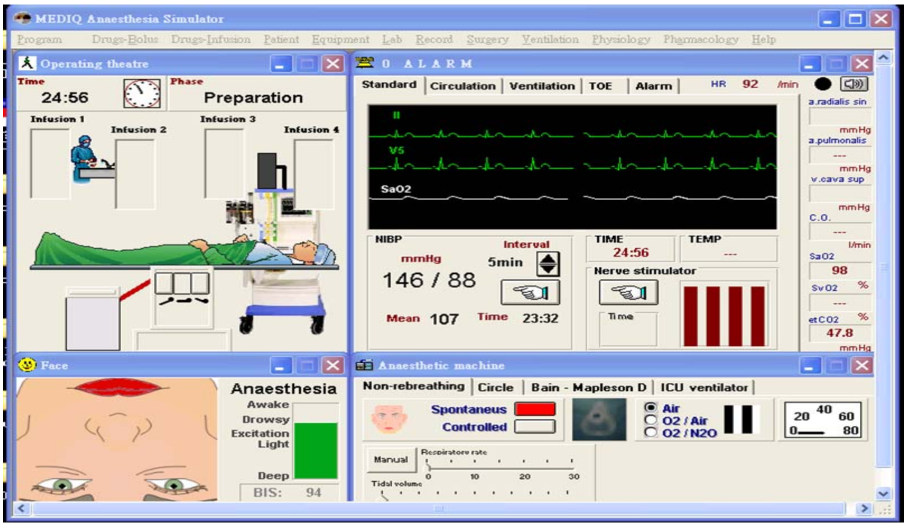

Fig. 2.8 The front panel of MEDIQ Anesthesia Simulator. User can monitor and operate with real-time patients responses.

2.6. Statistics

A pilot experiment has been implemented to let us preliminary understand the performance of proposed method during the anesthesia procedure. To achieve this, we compare the performance of our method with an authorized anesthesiologist with more than fifteen-year experience.

The performance index are **MAE** (mean absolute error of the BIS target), **PTAB** (percentage of acceptable BIS range), **RT** (recovery time), and drug consumption. The anesthesia conditions were set at BIS target 60, 50, and 40. Ten cases were implemented at each condition. The group average and standard deviation of each index, denoted as Mean $\pm$ Std, are used to be a criterion.

After the experiment, the results were fed into G*power (statistic program) to compute the appropriate sample size for distinguishing the performance of these two method. In the condition of BIS target is 60, there are twenty samples were needed. The extended experiment was implemented for the ten more examples. The test for the statistically significant is T-test (2-14).

$$t = \frac{\overline{D}}{S_D / \sqrt{n}}, df = n - 1 \tag{2-14}$$

2.7. A virtual anesthesiologist

The concept of our proposed method is to develop a virtual anesthesiologist. The idea of the virtual anesthesiologist is to help the clinicians, anesthesia or sedation practitioner, or even the anesthesiologist who is lack of experiences. According to the literature study we have done so far, the reason of inappropriate anesthesia level was due to the inappropriate administration of anesthetic drugs. The virtual anesthesiologist should contain the knowledge of the senior anesthesiologist and should perform well in the drug administration. It operates at the induction and maintenance stage of the anesthesia (as shown in Fig. 2.9).

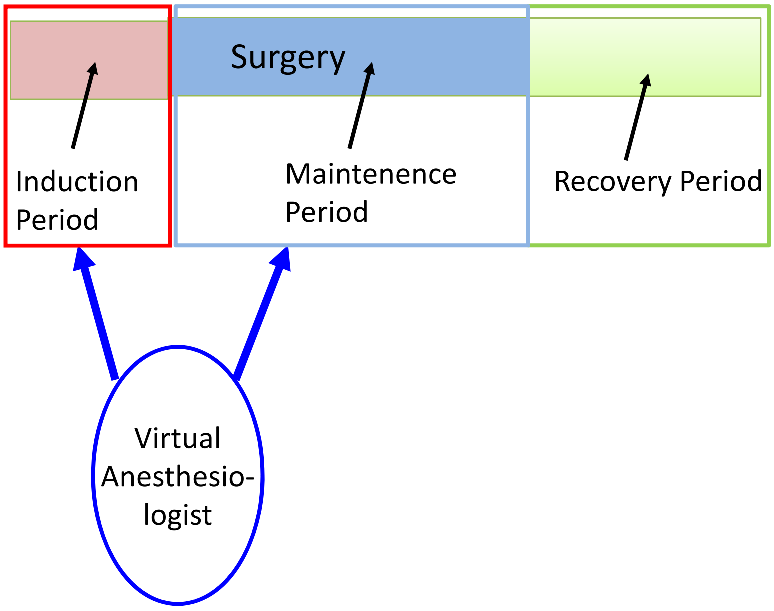

Fig. 2.9 The virtual anesthesiologist operate on induction and maintenance phase

The fashion it works would be like a consultant. It takes the physiological information of the patient as input and evaluates the suggestive value of the drug administration. The anesthesia/sedation practitioner takes its advices in the administration of anesthetic drugs. We show it in Fig. 2.10

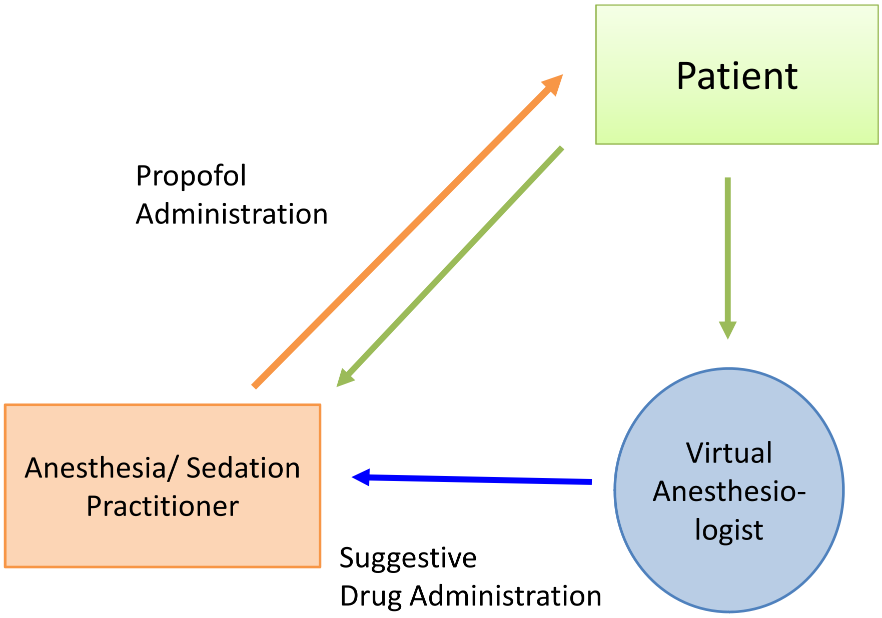

Fig. 2.10 Virtual anesthesiologist as a consultant

2.8. System architecture

The design of our virtual anesthesiologist can be treat as an anesthesia controller in this stage. It takes physiological signals as input and output the suggestion value of the propofol administration (ml/h).

The control target is target of **BIS** (**BIS**$_{\textbf{target}}$), which is the target (or the goal) that the Bispectral index of the patient should be maintained during the surgery procedure. As we mentioned in the previous section, **BIS** is the index of the DOA. That is the reason that we use **BIS** as our control variable. The architecture and the input/out variable of the system are shown in **Fig. 2.11.**

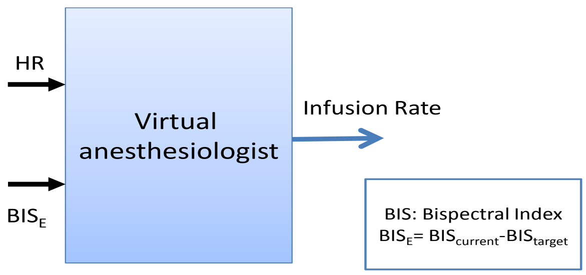

Fig. 2.11 Input/output variables of the virtual anesthesiologist

2.9. Virtual anesthesiologist design

As seen in Fig. 2.11, the core of our virtual anesthesiologist. There are no well defined standard in maintaining the DOA and that is the reason that accumulated experience of a senior anesthesiologist is so precious. We realize that the most efficient way is to mimic the thinking of the senior anesthesiologist in the drug administration.

In order to achieve this goal the design of the virtual anesthesiologist is to (1) accommodate the knowledge of the anesthesiologist, and (2) mimic the thoughts of the anesthesiologist in the drug administration. Based on these reasons we choose the neuro-fuzzy structure in the design of our virtual anesthesiologist because of its learning ability and the fuzzy inference characteristic. The structure of virtual anesthesiologist is shown in Fig. 2.12.

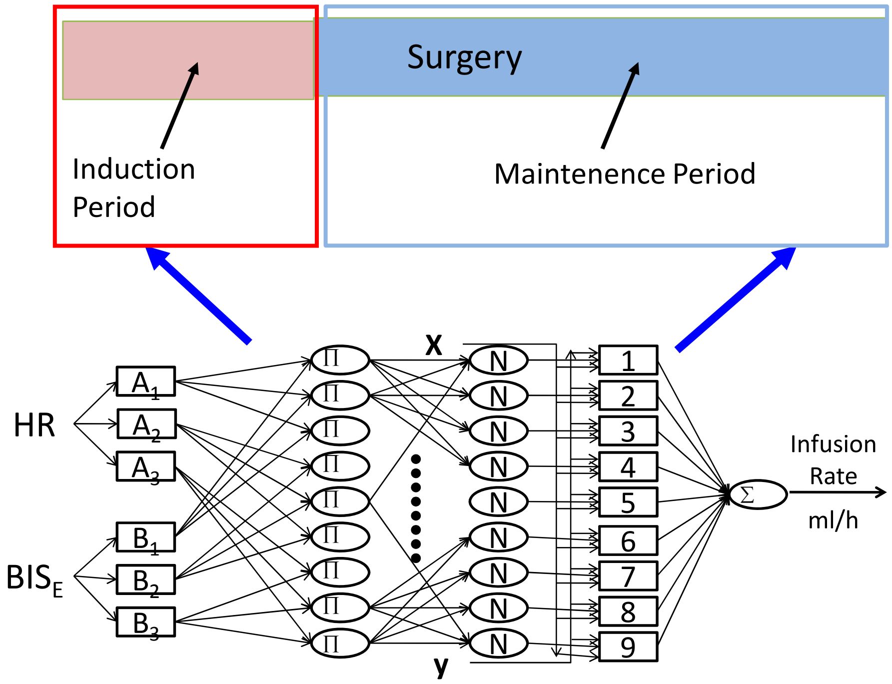

Fig. 2.12 ANFIS is used in virtual anesthesiologist

As shown in Fig. 2.12, the virtual anesthesiologist is based on the ANFIS inference structure. The training of the ANFIS is separate into two modes, one is trained by the data recorded during the induction phase and the other is by the maintenance phase. The anesthesia/sedation practitioner uses the former during the induction phase, and the latter during the maintenance phase. The training data is gathered by recording one anesthesiologist with more than fifteen-year experience. The data is recorded in the form of (**HR**, **BIS$_E$**, and drug administration, ml/h).

The main reason that the ANFIS is designed to be in separate model is that the purpose of the drug administration is different in these two phases. When in induction phase, the purpose is to anesthetize the patient to the depth which is suitable for carrying out the surgery and facilitate the intubation. But in the maintenance phase the purpose is to maintain the depth.

Chapter 3. Experiments and results

3.1. Experimental design and experimental environment

The purpose of the experiment is to examine the performance of our design which is the virtual anesthesiologist in the whole anesthesia procedure. The following of this section will describe the experiment design and the experimental environment. The descriptions of experimental environment are as follows,

1. **Simulated patient:** Mediq Anesthesia Simulator
2. **Anesthetic drug:** The anesthetic drug is propofol.
3. **Operation procedure:** the anesthesia procedure of the virtual anesthesiologist is operated by non-qualified anesthesiologist. The virtual anesthesiologist evaluates the drug administration every minute.
4. **BIS target:** as we describe in the previous section, BIS ranging from 40 to 60 is suitable for carrying out general anesthesia, we choose BIS target as 40, 50, and 60 to examine the performance of our virtual anesthesiologist.
5. **Sampling time:** at induction phase, we record data every 30 seconds, while at the maintenance phase the data is recorded every minute.

The results of our system are compared with the results of the anesthesiologist. The objective is to see how the performance is of the system with the real anesthesiologist under similar environment.

Comparison Index:

The index of the performance comparison is introduced and described in the following:

1. **MAE:** the mean absolute error between $\mathbf{BIS_{target}}$ and current BIS value.

$$\frac{\sum_{i=1}^{N}\left|BIS_{target} - BIS_{current}\right|}{N} \qquad (3\text{-}1)$$

where N is sample size and $\mathbf{BIS_{current}}$ is the current BIS value.

2. **PTAB ($\mathbf{BIS_{target}}$ ± 10):** the percentage of time for $\mathbf{BIS_{current}}$ between acceptable $\mathbf{BIS_{target}}$ ± 10 ranges.
3. **Recovery Time:** the time from drug infusion beginning to the patient opening eye.
4. **Drug Consumption:** the total anesthetic drug (propofol) consumption.

MAE and **PTAB** are the indexes that relate to BIS. BIS is the index itself in accessing the DOA as we described in the previous section, therefore it can be used as the index to access the performance of the anesthesiologist or the virtual anesthesiologist in the maintenance phase. Basically, smaller **MAE** represents the better performance in the maintenance phase, and bigger **PTAB** represents better performance. Smaller recovery time and the drug consumption stand for lower residues of the anesthetic drug on patients.

3.2. Pilot experiment result

We have carried out total 60 cases, In other words, 10 cases for each BIS target for anesthesia or virtual anesthesiologist (system operated by the non-anesthesiologist) operative procedure. Pilot experiment gives us a way to understand the behavior of our system. BIS data was recorded every case and the indexes were evaluated. The results of the pilot experiment are shown in Table 3.1 to 3.3, and Fig. 3.1 to 3.2. For each index, mean and stand deviation were evaluated.

Table 3.1 Results of the pilot study at BIS_{target} 60.

Patient	Virtual anesthesiologist (operate by non-anesthesiologist) MAE	PTAB (50-70, %)	Drug Cunsumption (ml)	Recovery Time (sec)	Anesthesiologist MAE	PTAB (50-70, %)	Drug Cunsumption (ml)	Recovery Time (sec)
1	2.56	100.00	34.98	1523.0	3.78	97.56	29.75	794
2	1.65	100.00	57.22	1847.0	2.52	97.50	29.77	784
3	1.2	100.00	35.14	1917.0	3.56	100.00	30.26	836
4	0.88	100.00	36.64	1924.0	4.72	87.50	28.06	885
5	0.92	100.00	36.18	1886.0	5.44	97.56	26.42	1182
6	1.02	100.00	35.21	1875.0	7.39	82.93	24.63	710
7	2.42	100.00	34.36	1999.0	3.87	97.44	27.24	944
8	1.52	100.00	37.08	1948.0	5.46	90.24	25.91	654
9	1.55	100.00	36.35	1918.0	6.02	85.37	24.51	827
10	1.35	100.00	34.86	1953.0	6.17	97.56	26.48	1407
Mean	**1.51**	**100.00**	**37.80**	**1879.0**	**4.9**	**93.37**	**27.30**	**902.3**
± Std	**±0.58**	**±0.00**	**±6.88**	**±132.3**	**±1.47**	**±6.21**	**±2.10**	**±228.4**

Table 3.2 Results of the pilot study at BIS_{target} 50.

Patient	Virtual anesthesiologist (operate by non-anesthesiologist) MAE	PTAB (40-60,%)	Drug Consumption (ml)	Recovery Time (sec)	Anesthesiologist MAE	PTAB (40-60, %)	Drug Consumption (ml)	Recovery Time (sec)
1	4.2	87.50	50.46	2507	2.78	97.56	46.13	1333
2	7.46	72.95	56.30	2607	3.55	92.50	40.35	1162
3	6.38	75.00	56.84	2817	5.12	97.56	50.69	1303
4	6.68	72.50	60.88	2798	3.39	97.56	47.59	1441
5	8.60	57.50	78.20	2988	4.10	97.50	45.02	1434
6	4.42	100.00	47.87	2378	5.35	95.00	43.39	1447
7	6.51	68.29	58.73	2636	3.78	87.80	43.03	1241
8	4.41	100.00	49.55	2360	3.62	92.86	46.89	1288
9	3.62	97.50	50.71	2549	3.02	97.44	41.99	1506
10	6.22	72.50	57.98	2705	8.20	95.12	39.43	1613
Mean	**5.85**	**80.26**	**56.75**	**2634.5**	**4.29**	**95.09**	**44.45**	**1376.8**
±Std	**±1.61**	**±14.94**	**±8.75**	**±198.7**	**±1.60**	**±3.24**	**±3.48**	**±135.2**

Table 3.3 Results of the pilot study at BIS_{target} 40

	Virtual anesthesiologist (operate by non-anesthesiologist)				Anesthesiologist			
Patient	**MAE**	**PTAB (30-50, %)**	**Drug Consumption (ml)**	**Recovery Time (sec)**	**MAE**	**PTAB (30-50, %)**	**Drug Consumption (ml)**	**Recovery Time (sec)**
1	5.71	95.12	79.42	3233	2.22	100.00	77.61	2892
2	5.80	95.00	73.95	2856	2.98	100.00	70.43	1785
3	6.40	72.50	82.41	3241	5.85	90.00	60.73	
4	6.92	85.00	67.65	2952	7.08	86.84	60.07	1868
5	6.60	80.00	87.78	3399	5.51	87.80	66.76	2182
6	5.45	87.50	84.65	3530	6.22	78.05	62.92	1913
7	8.35	62.50	68.76	3088	8.83	60.98	56.84	1805
8	6.65	92.50	72.61		5.08	85.00	64.92	2002
9	5.30	82.50	78.92	3159	3.88	87.80	80.36	2316
10	5.62	97.50	77.00		4.20	97.50	74.23	2332
Mean	**6.28**	**85.01**	**77.32**	**3182.2**	**5.18**	**87.40**	**67.49**	**2121.7**
±Std	**±0.92**	**±11.13**	**±6.64**	**±221.3**	**±1.96**	**±0.12**	**±7.92**	**±356.2**

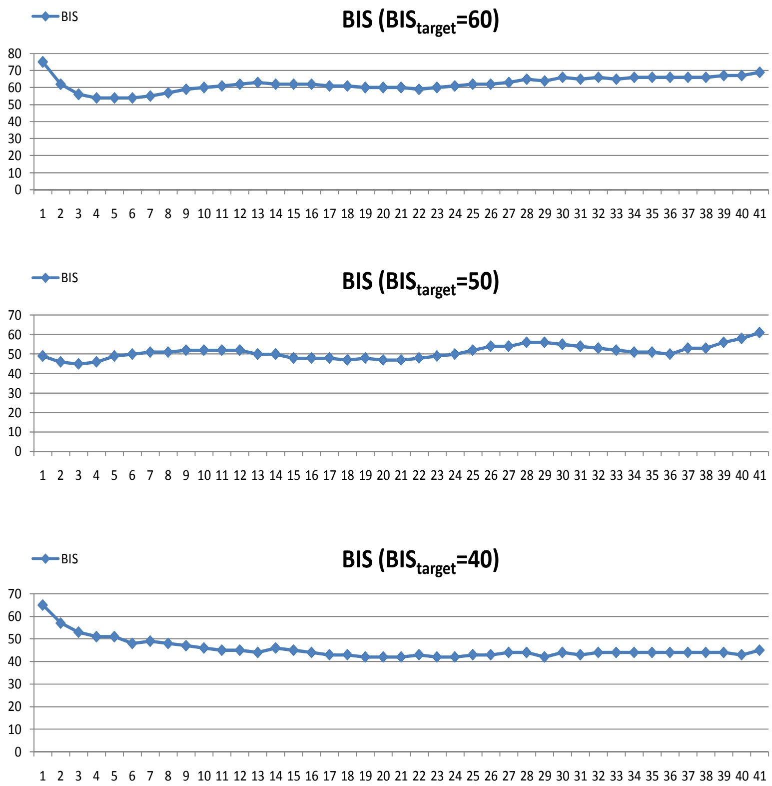

Fig. 3.1 Case example of BIS data recorded of real anesthesiologist. BIS_{target} is 60, 50, and 40.

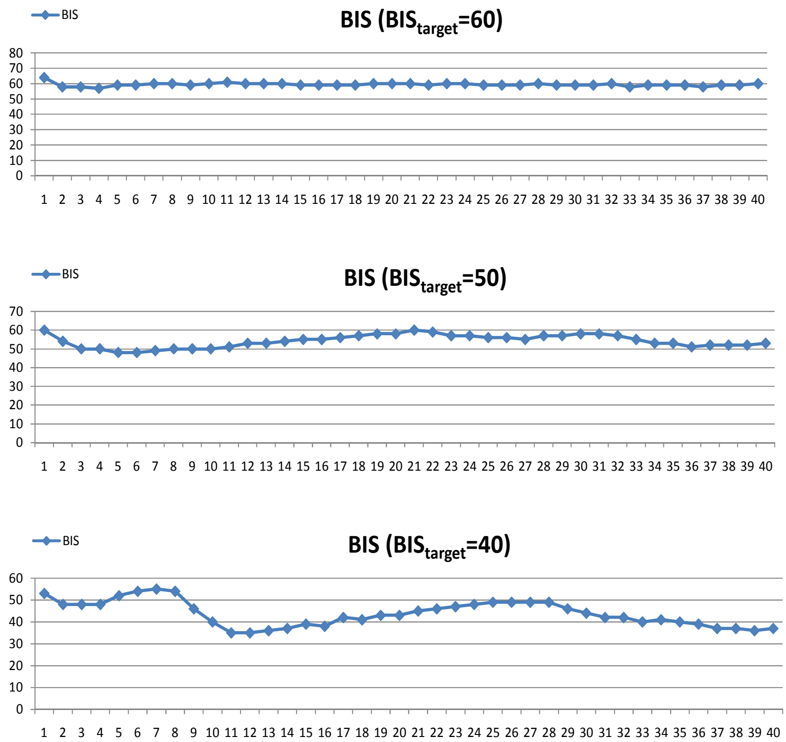

Fig. 3.2 Case example of BIS data recorded of virtual anesthesiologist. BIS_{target} is 60, 50, and 40.

3.3. Extended experiment result

The extended experiment was carried out after the pilot experiment. Through the understanding of the pilot experiment results and the evaluate consequences of the statistic program. We realize that in the condition of BIS target at 60. There are ten more cases needed for test for the statistic significant. The results of total 40 cases (20 for anesthesiologist operative cases and 20 for virtual anesthesiologist operative cases) and the results for the statistic significant test are shown Table 3.4 and 3.5.

Table 3.4 The results of the extended experiment results Where MAE is mean absolute error between BIS_{target} and current BIS value, and PTAB is the percentage of time for the acceptable BIS range

Patient	Virtual anesthesiologist				Real anesthesiologist			
	MAE	PTAB (50-70,%)	PTAB (55-65,%)	Recovery Time (sec)	MAE	PTAB (50-70,%)	PTAB (55-65, %)	Recovery Time (sec)
1	2.56	100.00	80.49	1523	3.78	97.56	65.85	794
2	1.65	100.00	92.50	1847	2.52	97.50	87.50	784
3	1.20	100.00	97.50	1917	3.56	100.00	75.61	836
4	0.88	100.00	100.00	1924	4.72	87.50	75.00	885
5	0.92	100.00	97.50	1886	5.44	97.56	46.34	1182
6	1.02	100.00	97.50	1875	7.39	82.93	24.39	710
7	2.42	100.00	87.50	1999	3.87	97.44	76.92	944
8	1.52	100.00	90.00	1948	5.46	90.24	65.85	654
9	1.55	100.00	92.50	1918	6.02	85.37	51.22	827
10	1.35	100.00	100.00	1953	6.17	97.56	26.83	1407
11	1.48	100.00	95.00	1933	2.12	100.00	87.50	902
12	0.88	100.00	100.00	1849	3.95	97.44	74.36	926
13	2.85	100.00	80.00	1920	3.78	95.00	82.50	600
14	7.12	80.00	60.00	2856	3.46	95.12	78.05	735
15	2.12	100.00	85.00	1897	3.75	100.00	75.00	994
16	2.18	100.00	82.50	1860	4.15	92.50	70.00	772
17	1.98	100.00	87.50	1957	2.95	100.00	85.36	1066
18	0.62	100.00	100.00	1932	2.95	100.00	80.49	811
19	1.00	100.00	100.00	1913	2.12	100.00	97.50	884
20	9.18	0.65	30.00	2312	3.48	100.00	77.50	757
Mean ± Std	2.22 ± 2.14	97.25 ± 8.81	87.77 ± 16.84	1961.0 ± 249.4	4.08 ±1.40	95.68 ±5.27	70.19 ± 9.24	873.5 ± 185.6

Table 3.5 Paired t-test analysis of the two control methods (anesthesiologist and virtual anesthesiologist), *P*<0.05 was considered statistically significant for anesthesiologist vs. virtual anesthesiologist using paired t-test.

	Virtual Anesthesiologist	**Anesthesiologist**	***P*-value**
BIS_{target} =60			
MAE	2.22±2.14	4.08±1.40	0.007393
PTAB (50-70,%)	97.25±8.80	95.68±5.27	0.530757
PTAB (55-65,%)	87.77±16.84	70.19±19.24	0.01104
Recovery Time (sec)	1961.0±249.4	873.5±185.6	7.53E-12

Table 3.5 shows the results after the paired t-test of the extended experiments. The operation results of the virtual anesthesiologist are compared with the results of the anesthesiologist. The *P*-value which smaller than 0.005 indicates the results of the two control methods is statistic significant of that performance index.

Chapter 4. Discussion and conclusion

4.1. Employing anesthesia simulator into the experiment

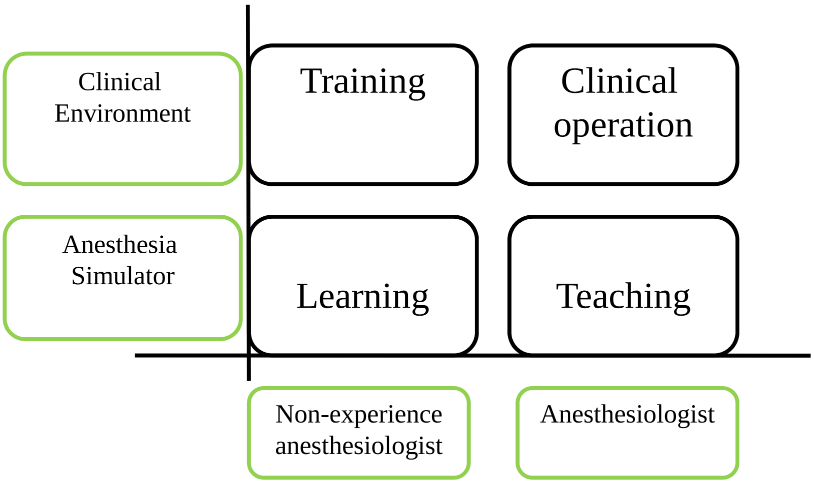

Fig. 4.1 Anesthesia simulator in teaching and learning

We employed the anesthesia simulator into the procedure of our experiment. The environment and the patients are all simulated. Anesthesia simulator has been adopted into training procedures of the anesthesiologist in many medical centers or university-teaching hospitals. Not only the high fidelity but also the low fidelity anesthesia simulators become more and more popular [33].

The limitation or the characteristic of the anesthesia simulator is that no anesthesia simulator is completely realistic. There are many details and variances in human body and the surgical procedure that the simulator cannot simulate presently. Even though, this characteristic gives simulator has the ability to be a intermediate platform between the off-line data and the clinical environment.

As described in the previous section, anesthesia simulator has been adopted in training and teaching of anesthesia. The presentation of the simulator can be illustrated in Fig.4.1. It can be used in teaching, training, and learning.

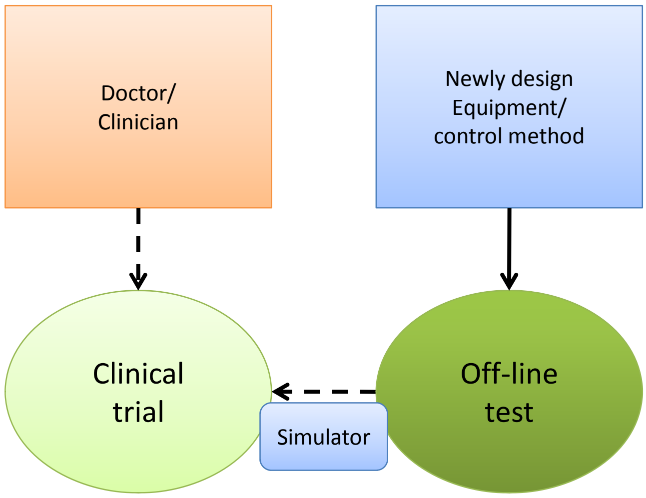

Fig. 4.2 The traditional path of verification or validation of the equipment

The traditional path of verification or validation of the equipment (for example anesthesia drug administration controller or the monitor interface) in the medical engineering field can be shown in Fig. 4.2. New equipment is validated off-line then applying for clinical trial. During the clinical trial the performance is compared with the procedure operated by the doctor or the original equipment.

The characteristic of the intermediate fidelity of the anesthesia simulator make it has the benefits when employing into the validation path. The performance of the equipment can be validated in the environment more resemble to the real clinical environment. Moreover, the doctor or the clinicians can join the validation procedure.

It can make us understand the equipment more before into the clinical trial.

4.2. Discussion of the results

The following of the section will discuss the results of the experiment. The results will be discussed in the aspect of the performance indexes introduced in chapter 3 (**MAE**, **PTAB**, drug consumption, and recovery time).

4.2.1. Pilot experiment results

1. The performance of the virtual anesthesiologist:

Table 4.1 The performance of the virtual anesthesiologist.

BIS_{target}	MAE	PTAB (BIS target ±10, %)	Drug Consumption (ml)	Recovery Time (sec)
60	1.50 ± 0.58	100.00± 0.00	37.80 ± 6.88	1879.0 ± 132.3
50	5.85 ± 1.61	80.25 ± 14.94	56.75 ± 8.75	2634.5 ± 98.73
40	6.27 ± 0.91	85.01 ± 11.13	77.31 ± 6.64	3182.25± 221.36

We can see from Table 4.1 the virtual anesthesiologist performed well control of DOA as $\mathbf{BIS_{target}}$ is 60 (from the results of **MAE**) and then the performance decrease as BIS is 50 and 40. This result reveals that the structure of the virtual anesthesiologist currently prefers lighter DOA. The drug consumption and recovery time are reasonable the deeper the depth of the anesthesia is, the more drug and recovery time is required for the anesthesia procedure.

2. The performance of the real anesthesiologist:

Table 4.2 The performance of the anesthesiologist with more than fifteen-year experience.

BIS_{target}	MAE	PTAB (BIS_{target} ± 10, %)	Drug Consumption (ml)	Recovery Time (sec)
60	4.89 ± 1.47	93.36 ± 6.21	27.30 ± 2.10	902.3 ± 228.4
50	4.29 ± 1.60	95.09 ± 3.23	44.45 ± 3.48	1376.8 ± 135.2
40	5.17 ± 1.96	87.40 ± 11.63	67.49 ± 7.92	2121.7 ± 356.2

We can see from Table 4.2 that the anesthesiologist performed similar performance as **BIS_{target}** is 60, 50, and 40. That suggests that the knowledge and the operation behavior will not be affected by the target DOA in the maintenance phase. The drug consumption and the recovery time are still reasonable.

3. The comparison of the performance of the virtual anesthesiologist with real anesthesiologist:

Table 4.3 The comparison of the performance of the virtual anesthesiologist with the real anesthesiologist under BIS_{target} = 60, 50, and 40. The results is expressed in the form of Mean ±Std . Where MAE is mean absolute error between BIS_{target} and current BIS value, and PTAB is the percentage of time for BIScurrent between acceptable BIStarget ± 10 ranges.

BIS target	MAE		PTAB (BIS target±10 ,%)		Drug Consumption (ml)		Recovery Time (sec)	
	VA	A	VA	A	VA	A	VA	A
60	1.50 ±0.58	4.89 ±1.47	100.00 ±0.00	93.36 ±6.21	37.80 ±6.88	27.30 ±2.10	1879.0 ±132.3	902.3 ±228.4
50	5.85 ±1.61	4.29 ±1.60	80.25 ±14.94	95.09 ±3.23	56.75 ±8.75	44.45 ±3.48	2634.5 ±198.73	1376.8 ±135.2
40	6.27 ±0.91	5.17 ±1.96	85.01 ±11.13	87.40 ±11.63	77.31 ±6.64	67.49 ±7.92	3182.25 ±221.36	2121.7 ±356.2

From the aspect of MAE and PTAB, the real anesthesiologist performed better than our virtual anesthesiologist as **BIS_{target}** 50 and 40, but as **BIS_{target}** is 60, our virtual anesthesiologist performed much better than real anesthesiologist. The drug consumption and recovery time indicates that real anesthesiologist used less anesthetic drug (propofol) than our virtual anesthesiologist. We observed that the real anesthesiologist tends to stop or reduce the drug infusion when the surgery in come to an end. That maybe the reason of **MAE** performance as **BIS_{target}** 60. The design of operation of our virtual anesthesiologist did not accommodate this kind fashion.

4.2.2. Extended experiment results

Table 4.4 The result of the extended experiment (BIS_{target} as 60).

	Virtual Anesthesiologist	Anesthesiologist	*P*-value
BIS_{target} =60			
MAE	2.22±2.14	4.08±1.40	0.007393
PTAB (50-70,%)	97.25±8.80	95.68±5.27	0.530757
PTAB (55-65,%)	87.77±16.84	70.19±19.24	0.01104
Recovery Time (sec)	1961.0±249.4	873.5±185.6	7.53E-12

From the pilot experiment the extended cases was carried out to test for the statistic significant. In the aspect of **MAE**, which reflects the performance of the maintenance phase, statistic shows the statistic significant and the result of the virtual anesthesiologist is better than the real anesthesiologist. But as for the aspect of **PTAB** (acceptable BIS range 50-70) there were no statistic significant. We tightened the acceptable BIS range to 55-65 (which is 60 ± 5), the statistic test shows the significant and the result of the virtual anesthesiologist is better than the real anesthesiologist. At the aspect of the recovery time, it somehow reflects the drug consumption, the result of the real anesthesiologist is better than the virtual anesthesiologist.

We can observe from the extended experiment that there are some shortcomings of our virtual anesthesiologist. For example if there are some critical situation of the **HR** of the patient (it is also the input variable of the virtual anesthesiologist), the virtual anesthesiologist could not handled that and will cause untoward results of the drug administration.

The result of the extended experiment makes us understand the behavior of the newly designed virtual anesthesiologist before attending into clinical trial. For example we can make adjustments to our design of the system architecture under the environment that is more resemble to the clinical environment. It is benefit for attending the clinical trial.

4.3. The case and the simulator

The following section we will discuss two issues. The case (simulated patient) we choose in the anesthesia simulator for our research and the characteristic of the simulator itself.

The case (simulated patient) we choose in the anesthesia simulator is a thirty-two years old young man with the Arthroscopy. The information and the description of the simulated patient is shown in Table 4.5.

The main reason we choose this kind of surgery condition is that the surgical time (about 38~40 minutes) is longer enough for testing the purpose of maintenance the DOA during the surgical time without the unnecessary mistake caused by human factors result from the fatigue of long working hours.

The depth of anesthesia needed for this surgery is contrast lighter. Lighter depth relate to less consumption of the anesthetic drug and smaller variance cause by the drug. That may be the reason that the performance of the virtual anesthesiologist in the BIS_{target} 60 condition is better than the other two BIS_{target} conditions.

Table 4.5 Information and the description of the simulated patient case in the research.

Length	182 cm
Weight	69 kg
Hematocrite	32 %
Creatinine	86 μM
Brief description of the patient	
The 32 years old man is healthy apart from migraine and a whiplash-trauma in a car accident a few years ago causing radiating pain from the cervical region. His right knee is unstable, often swollen and sometimes "locked" since he fell in a soccer match two months ago.	

The cases in the experiment of the research all choose this simulated patient case. One of the characteristics of the simulator is that all cases have slight differences in the surgical situation and the patient responses. Which make all cases can be treated as similar but independent case. For example, the simulator randomly produces some events which are abnormal in the surgical progress. One of them is shown in Fig. 4.3. Which **HR** significantly abnormal change has no direct relation to propofol administration.

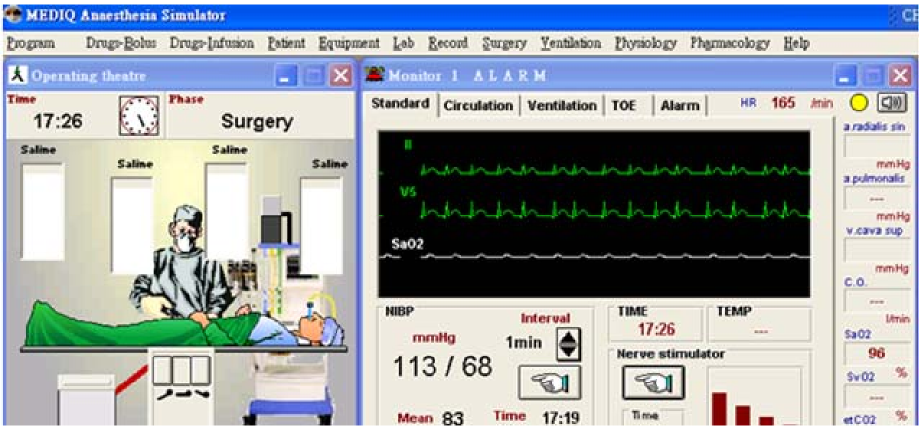

Fig. 4.3 One of the abnormal events that simulator randomly produced

Chapter 5. Conclusion and future works

5.1. Conclusions

We have designed and implemented an assistant system, which takes **HR** and **BIS** information of the patient as the input variables and evaluates the suggestive propofol infusion rate. As an intermediate platform for the preliminary test of the newly developed before going into the clinical trial, the anesthesia simulator has been employed into the experiment design and has exposed its value. The pilot and the extended experiments have been carried out. Three conditions, BIS target 60, 50, and 40, of the pilot experiments has been set. BIS target 60 is the extended experiment. The result have showed that under the current experiment environment (the environment is limited) the virtual anesthesiologist has the ability to anesthetize and maintain the patient at a certain level of anesthesia. But we can also discover that the virtual anesthesiologist has its own shortcomings. The future works have been discussed in the following section.

5.2. Future works

1. **The Input variable:** the input of the virtual anesthesiologist currently is **HR**, and the $\mathbf{BIS_E}$ ($\mathbf{BIS_{current}}$ - $\mathbf{BIS_{target}}$). We can see from the experiment that virtual anesthesiologist had better performance at BIS target is 60 than is 50 and 40. The reason may be that the value of $\mathbf{BIS_E}$ is too rough. For example the $\mathbf{BIS_E}$ is the same at $\mathbf{BIS_{current}}$ is 64 ($\mathbf{BIS_{target}}$ is 60) and $\mathbf{BIS_{current}}$ is 54 ($\mathbf{BIS_{target}}$ is 50), but the situation and the drug needed to maintain the anesthesia level is quite different.

Table 5.1 The comparison of the performance of the virtual anesthesiologist with the real anesthesiologist under BIStarget = 60, 50, and 40. The results is expressed in the form of Mean ± Std . Where MAE is mean absolute error between BIStarget and current BIS value, and PTAB is the percentage of time for BIScurrent between acceptable BIStarget ± 10 ranges.

BIS target	MAE		PTAB (BIS target ± 10 ,%)		Drug Consumption (ml)		Recovery Time (sec)	
	VA	A	VA	A	VA	A	VA	A
60	1.50 ± 0.58	4.89 ± 1.47	100.00 ± 0.00	93.36 ± 6.21	37.80 ± 6.88	27.30 ± 2.10	1879.0 ± 132.3	902.3 ± 228.4
50	5.85 ± 1.61	4.29 ± 1.60	80.25 ± 14.94	95.09 ± 3.23	56.75 ± 8.75	44.45 ± 3.48	2634.5 ± 198.73	1376.8 ± 135.2
40	6.27 ± 0.91	5.17 ± 1.96	85.01 ± 11.13	87.40 ± 11.63	77.31 ± 6.64	67.49 ± 7.92	3182.25 ± 221.36	2121.7 ± 356.2

2. **The operation strategy:** we can see from the results that the drug consumption and the recovery time needed of the virtual anesthesiologist is larger than real anesthesiologist. The reason may be that the real anesthesiologist prefers to stop or reduce the drug infusion before the surgery ended rather than retain the BIS level. On the other hand our virtual anesthesiologist focuses the goal on maintain the BIS value at the target of BIS until the surgery ended. The modification of the operation strategy of the virtual anesthesiologist needs to be further discussed and surveyed.

3. **Wider experiments:** the current tests or the validations of the virtual anesthesiologist are in limited conditions. For example the simulated patient is limited on very similar situation and the lack of comparison with other controller method. For the validation and the goal of practical usage, the wider experiments are needed in the future.

Reference

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