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# Automating Intravenous Anaesthesia with a Fuzzy Inference System Coupled with a Proportional Integral Derivative (PID) Controller

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## Abstract

Current situation in operation theatre is that anaesthesiologist is monitoring different physiological parameters, judging depth of anaesthesia and regulating drug rate manually. This manual drug dosing may go overdose or under-dose, as it depends upon experience and skill of anaesthesiologist. Under-dosing causes patient to feel pain. Overdosing may lead to unconsciousness leading to death. Automatic drug dosing will help anaesthesiologist to focus on more critical issues such as blood loss etc. In this focus, anaesthesia, when thought of as a multivariate, non-linear, and complex process fraught with uncertainties and handled by experts, can be mapped using fuzzy logic. A proportional integral derivative (PID) controller has proved useful in all types of industries. A novel approach is proposed involving a fuzzy inference system, which monitors the status of the patient, coupled with a PID controller, for closed-loop control of intravenous anaesthesia. By automating anaesthesia, ultimately total amount of drug infused is reduced and hence it results into fast recovery. One more advantage of automating it is that post anaesthesia side-effects will be reduced. A simulation with ten virtual patients showed that the proposed approach offered reliable control of the process and tracked input signals accurately despite the variations from patient to patient and disturbances to the system.

## 1. Introduction

For complex processes such as anaesthesia, which are handled by experts, modelling the uncertainties in the process is a difficult task. In such processes, the level of accuracy can be expressed by characterizing and quantifying the uncertainty. As the process becomes more complex, so does the degree of inexactness of information. Therefore, it is desirable to determine the relationship between precision, information, and complexity. Most processes, however, can be controlled better despite some imprecision, and fuzzy logic seeks to map imprecision and uncertainty with the help of experts to control a complex process.

Conventional proportional integral derivative (PID) controllers are well established and have found applications in different fields for more than fifty years. However, the conventional PID controller fails to work for non-linear and higher-order systems when used alone. The metabolism of anaesthetic drugs is highly complex and non-linear but readily lends itself to being characterized effectively as a linear system that can be inexpensive, easy to design, simple to operate, and economical to maintain.

Pharmacokinetics and pharmacodynamics can model the distribution of the drug within a body, the metabolism of the drug, and its effects, all of which vary dynamically, depending on the individual to whom it has been administered. This variation tends to make the process a higher-order system, which is less amenable to being controlled with a conventional PID controller. On the other hand, the ability of a fuzzy inference system (FIS) to store expert knowledge, when combined with the advantages of a PID controller, offers a more reliable means to control the process of administering intravenous anaesthesia.

Researchers have been working for more than fifty years to automate the process of administering anaesthesia, a highly specialized procedure during which changes in more than a hundred parameters have to be monitored constantly—rapid and appropriate responses to which often mean the difference between a positive outcome and an adverse one [13]. Krol and Reich, in 2000, developed a decision-support system to detect such clinical conditions as light anaesthesia or unstable blood pressure based on three parameters, namely heart rate (HR), mean arterial pressure (MAP), and systolic arterial pressure [23]. Dunsmuir et al. went farther and, in 2008, developed a knowledge-authoring tool to support clinical decisions: the tool had the ability to incorporate appropriate knowledge-based rules on its own without a knowledge engineer or a programmer [20]. The knowledge-authoring tool developed by Krol et al. [13], although simple, was a significant step towards introducing expert systems into clinical monitoring and, in turn, into automated control of medical procedures. Morari and his team have also contributed significantly to the effective control of anaesthesia [16, 17]; they showed how a model predictive controller can be used to administer the sedative propofol based on transcutaneous partial pressure of carbon dioxide, a non-invasive measure of gas-based anaesthesia. In 2010, Mirza et al. [15] reported a fuzzy-logic-based diagnostic alarm system for detecting critical events while administering anaesthesia. Successful application of this alarm system promoted the idea of a closed-loop control of anaesthesia using fuzzy logic.

Hemmerling and his team at McGill University in Canada [18] compared manual and automated administration of anaesthesia using Bispectral Index (BIS) as the controlled variable and concluded that the automated system offered more precise control of the process, keeping the depth of anaesthesia closer to the desired level than that achieved manually. In 2011, they published a paper explaining the principles governing 'Mcsleepy', the name they gave to the automated system [14]. Mcsleepy provides automated control of anaesthesia but needs to know the stage of surgery at any given moment. The controller is based on 'analgoscore', a measure based on HR and blood pressure and similar to the standard pain score system used for patients who are awake, which indicates the patient's response to pain during surgery. In another paper, Dr Hemmerling and co-workers reviewed decision-support systems in anaesthesia, emergency medicine, and intensive care [13] and designed a knowledge- and rule-based decision-support system to improve outcomes. They also developed the Kepler intubation system in 2012 [8, 9] and evaluated a novel closed-loop total intravenous anaesthesia drug delivery system using a randomized control trial. The system used BIS and analgoscore as controlled variables [7]. It should be mentioned, however, that the use of BIS for hypnosis control is controversial [18].

More recently, in 2015, Chang and co-workers published a detailed review titled 'Automation of anaesthesia: a review on multivariable control' [1], in which they discuss several significant challenges to automating anaesthesia including uncertainty, controlled variables, closed-loop application, safety, and reliability to conclude that it is desirable to develop control strategies to regulate all the necessary components of anaesthesia simultaneously with balanced use of various drugs.

The present paper builds on the work reported so far to design and implement a FIS that monitors the state of the patient and is coupled with a PID controller for closed-loop control of intravenous delivery of anaesthetic drugs. A block diagram of the proposed system is shown in Fig. 1. An infusion pump delivers the drug, and changes in its concentration in body fluids are reflected in such physiological parameters as MAP, HR, and oxygen saturation (OXSAT). These parameters can act as measures of the depth of anaesthesia (DOA), which is compared to the set point (the reference DOA), and the calculated error is fed to the PID controller, which determines the appropriate action and actuates the control, namely the motor of the infusion pump, to regulate the rate at which the anaesthetic drug is being administered.

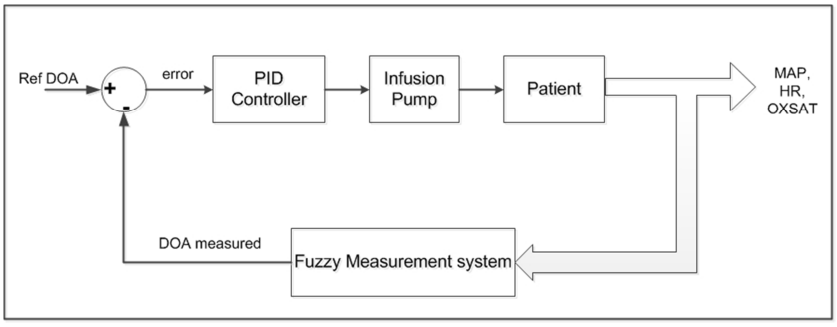



***Fig. 1.*** *Block diagram of the proposed system.*

## 2. A Pharmacokinetic–Pharmacodynamic Model

A pharmacokinetic–pharmacodynamic model describes the physiological effect of a drug. Pharmacokinetics describes the concentration of a drug in the human body after the drug has been distributed and cleared, whereas pharmacodynamics constitutes the effect of change in the concentration of the drug on physiological parameters.

### 2.1. Pharmacokinetics

Pharmacokinetics can be defined as the characterization and prediction of the course of the concentration of a drug in the body over time. The course is affected by how the drug is absorbed, distributed, metabolized, and finally eliminated from the body. Pharmacokinetics of anaesthetic drugs can be described by the three-compartment model shown in Fig. 2, in which $X_1$, $X_2$, $X_3$, and $X_e$ are the drug concentrations (mg/mL) in compartments 1, 2, 3, and at the effect site, respectively. $K_{ij}$ denotes the frequency of drug transfer from the $j^{th}$ to the $i^{th}$ compartment, and I(t) is the rate (mg/s) of infusion of the anaesthetic drug in the central compartment. Using this hydraulic model, the processes that decrease blood concentration over time can be correlated. Initially, the drug flows from the central compartment to both the peripheral compartments through inter-compartmental clearance and then out of the model through metabolic clearance.

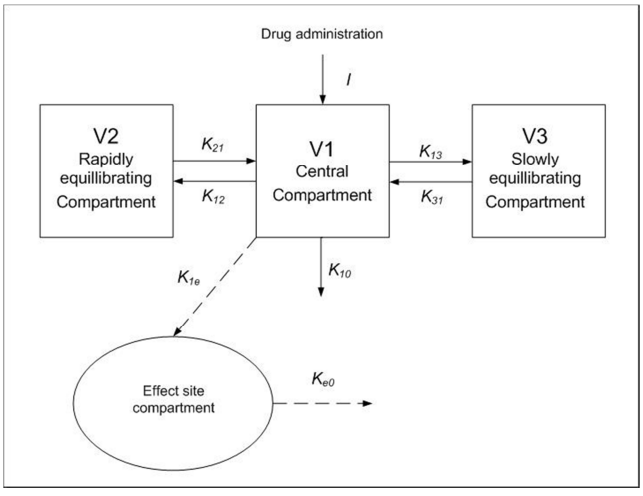



***Fig. 2.*** *The pharmacokinetic model.*

The compartment that represents the site of the drug's effect compensates for the time lag between the observed effect and the concentration of the drug in the plasma. The concentration of the drug in this theoretical compartment is directly related to the measured effect of the drug. The compartment receives the drug from the central compartment by a first-order process, expressed by the first-order rate constant $K_{e1}$. The actual mass of the drug reaching the effect compartment is negligible. The pharmacokinetic model is represented by the differential equations 1 to 4, which are given below.

$$\dot{x_1} = -[K_{10} + K_{12} + K_{13}].x_1(t) + K_{21}.x_2(t) + K_{31}.x_3(t) + \frac{I(t)}{V_1} \quad (1)$$

$$\dot{x_2} = K_{12}.x_1(t) - K_{21}.x_2(t) \quad (2)$$

$$\dot{x_3} = K_{13}.x_1(t) - k_{31}.x_3(t) \quad (3)$$

$$\dot{C} = K_{e0}(C_p - C_e) \quad (4)$$

### 2.2. Pharmacodynamics

Pharmacodynamics is the effect of the drug's concentration on physiological parameters; in other words, pharmacodynamics describe what happens to the human body after an anaesthetic drug is administered. The effect is defined by Equation 5.

$$E(t) = E_0 \pm (E_{max} - E0)\frac{C(t)^{\gamma}}{(C(t)^{\gamma} + EC_{50}{}^{\gamma})} \quad (5)$$

Where E(t) is the total effect on the parameter; $E_0$ is the parameter value when no drug is administered; $E_{max}$ is the maximum effect of the drug; C(t) is the concentration of the drug derived from pharmacokinetics; $\gamma$ is identical to Hill's Coefficient of the dose response curve; and $EC_{50}$ is calculated using Equation 6.

$$EC_{50} = \frac{ED_{50}}{K_n} \quad (6)$$

Whereas $ED_{50}$ is directly read from the dose response curve, $K_n$ is computed by using Equation 7.

$$K_n = \frac{D}{C_e(tpeak)} \quad (7)$$

Dose response curves for many drugs and for different groups of patients are available in the literature.

## 3. Fuzzy Theory

In general, a fuzzy logic system is a non-linear mapping of the input data (feature) vector onto a scalar output (the vector output decomposes into a collection of independent multi-input–single-output systems). The richness of fuzzy logic lies in the enormous numbers of possibilities that lead to many different mappings. This richness does require a careful understanding of fuzzy logic and the elements that comprise a fuzzy logic system (FLS). The main elements of a FLS are fuzzification, rule base, inference mechanism, and defuzzification, as shown in Fig. 3. Fuzzification is the process of human–machine precisiation and constitutes a mathematical representation of human interpretation. If X is a collection of objects x, then a 'fuzzy set' A in X is defined as a set of ordered pairs as given by Equation 8.

$$A = \{(x, \mu_A(x)) | x \in X\} \quad (8)$$

Where μA(x) is referred to as the 'membership function' (MF) for the fuzzy set A. The membership functions map

each element of X to a membership grade or membership value between 0 and 1. An expert's knowledgebase is stored in terms of MFs. In the present study, the knowledge base was collected from ten experts. Membership functions follow different shapes and rely on the plausibility of occurrence of an event or its linguistic representation. For example, when we say that the value of an antecedent is low, the probability that the antecedent is at its typical value will be highest, which is assigned the value of 1; the probability of the antecedent being at its typical value decreases as the value of the antecedent either increases or decreases. Input variables for a fuzzy inference system (FIS) are MAP, HR, and OXSAT whereas the output variable is the DOA. These antecedents and consequences are categorized as low, medium, and high based on the ranges collected from experts. Membership functions are calculated for all linguistic variables and thus constitute the expert's knowledgebase.

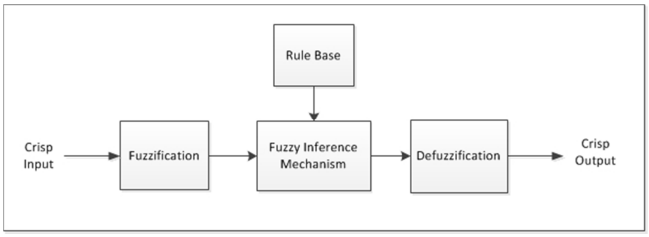



***Fig. 3.*** *Block diagram of a fuzzy system.*

The next component of a FLS is the rule base, which represents the experts' ability to make appropriate decisions reduced to a set of if–then rules. For instance, the *i*th fuzzy rule is given as follows:

- If $Z_1(t)$ is $M_1^i$ and $Z_2(t)$ is $M_2^i$ …and $Z_n(t)$ is $M_n^i$(fact)
- Then $C_1(t)$ is $W_1^i$ and $C_2(t)$ is $W_2^i$ …and $C_n(t)$ is $W_n^i$(Conclusion)

where $Z_1(t)$, $Z_2(t)$,…, $Z_n(t)$ are antecedents; $M_1^i$, $M_2^i$, …$M_n^i$ are linguistic representations of antecedents; $C_1(t)$, $C_2(t)$, … $C_n(t)$ are consequents, and $W_1^i$, $W_2^i$,…, $W_n^i$ are linguistic representations of consequences. Typical fuzzy rules are as follows:

1. If MAP is low and HR is low and OXSAT is low, then DOA is low.
2. If MAP is low and HR is low and OXSAT is medium, then DOA is low.

A fuzzy inference mechanism drives fuzzy rules for the observed values of the antecedents and calculates the fuzzified consequences. The present paper used the Zadeh–Mamdani inference mechanism, which is defined as follows.

Within the rule: (Consider Rule 1.0; Equation 9)

$$\mu_{W_1^i} = \min(\mu_{M_1^i}, \mu_{M_2^i}, \mu_{M_3^i}, \ldots \mu_{M_n^i}) \quad (9)$$

Between the rules (Equation 10)

$$\mu_{w1} = \max(\mu_{W_1^1}, \mu_{W_1^2}, \mu_{W_1^3}, \ldots \mu_{W_1^n}) \quad (10)$$

A fuzzified consequence is later defuzzified into a crisp value by defuzzification, and different methods are used for defuzzification. Using the centroid of an area is a widely used method because of its accuracy, which is given by Equation 11.

$$Z_{COA} = \frac{\sum \mu_A(Z).Z}{\sum \mu_A(Z)} \quad (11)$$

## 4. Controller Design

The most popular feedback controller used within the industry is the PID algorithm; used successfully for over fifty years, it is a robust and easily understood algorithm that provides excellent control despite the varied dynamics of the processes being controlled. The action of a PID controller is defined by Equation 12.

$$u(t) = K_p * e(t) + K_i \int e(t)dt + K_d * \frac{de(t)}{dt} \quad (12)$$

where $K_p$is the proportional gain;$K_i$is the integral gain; $K_d$is the derivative gain; and$e(t)$is the instantaneous error. For hardware implementation, this equation is converted into a discrete form (Equation 13).

$$u(k) = u(k-1) + a * e(k) + b * e(k-1) + c * e(k-2) \quad (13)$$

where

$$a = \left(K_p + K_i * \frac{T_s}{2} + \frac{K_d}{T_s}\right)$$

$$b = (-K_p + K_i * \frac{T_s}{2} - 2\frac{K_d}{T_s})$$

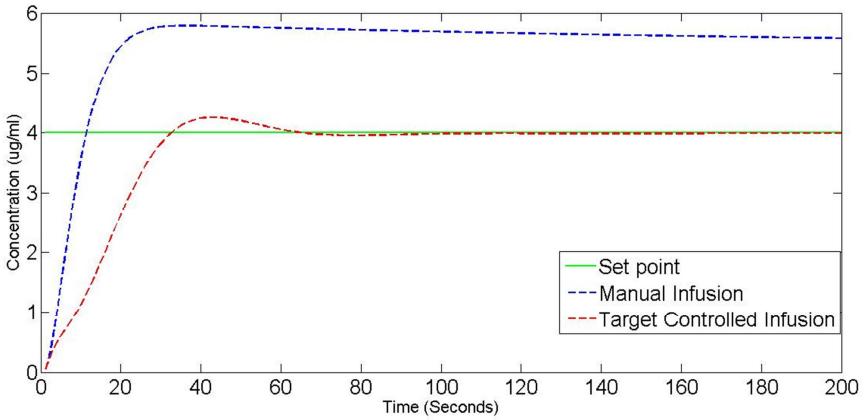
$$c = \frac{K_d}{T_s}$$

Tuning a controller involves the selection of optimum values of $K_p$, $K_i$, and $K_d$. The tuning seeks to match a predetermined ideal response profile for the closed-loop system. The Ziegler Nichols method was adopted here for tuning the PID controller.

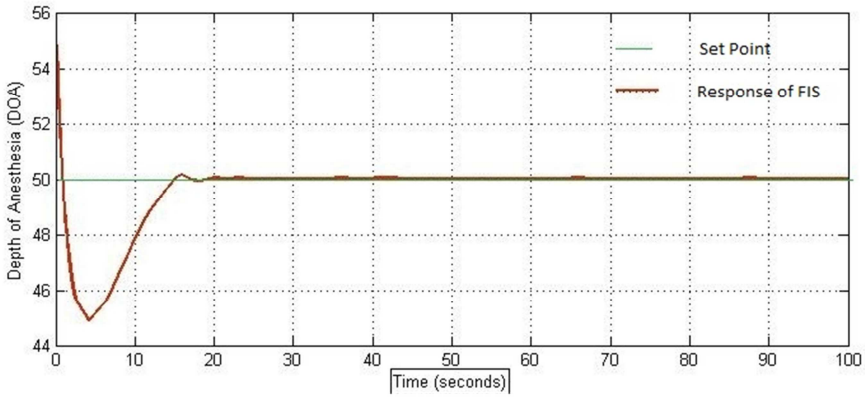
## 5. Results and Discussion

The proposed design was simulated at different stages using Matlab. Manual dosing was compared to the target-controlled infusion response, as shown in Fig. 4 (a). If the anaesthetic drug is administered manually, its concentration reaches 5.85µg/mL (shown in blue) whereas the expected range of concentration of propofol for hypnosis is 4–6 µg/mL [23]. If the drug concentration calculated by the patient model is used as a control variable and the PID controller is applied to administer anaesthetic drugs, the concentration is maintained at 4µg/mL (shown in red). The total amount of drug delivered is also less in the case of automated delivery. Although more advantageous than manual dosing, the automated method fails in situations such as blood loss during surgery, which can be monitored and controlled by direct or indirect measurement. Therefore, the multi-input–

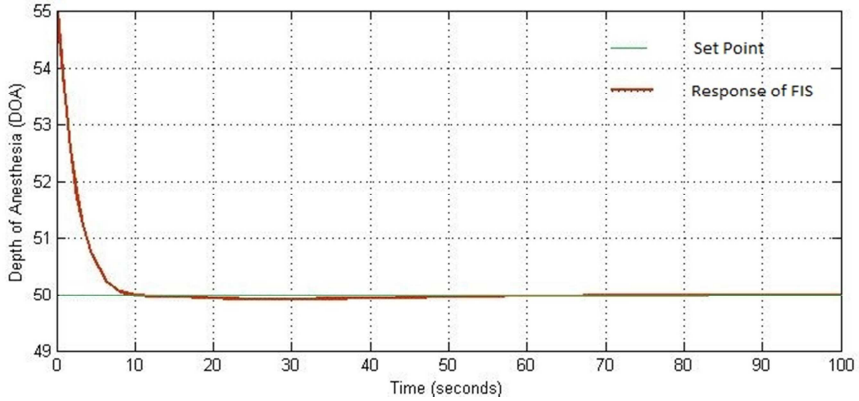
single-output FIS is designed to control the delivery of anaesthetic drugs. For the designed FIS, out of 270 sampled conditions, experts accepted 98.88% of the decisions made by the system as appropriate. The response of the FIS is as shown in Fig. 4 (b), seen as a negative peak (to be avoided). To overcome this problem, a PID controller was used in the loop. Fig. 4 (c) shows the response of the PID controller combined with a FIS. The designed strategy was implemented using Spartan 3E FPGA and tested with virtual patients. Schinder's pharmacokinetic model was used for simulating the responses of the virtual patients [24]. A total of ten patients (6 men and 4 women) were considered: the weights of patients ranged from 48 kg to 90kg; their heights, from 157 cm to 175cm; and their ages, from 22 years to 55years. The responses of the virtual patients are shown in Fig. 5. One can observe that the trajectory of the DOA is consistent with the desired trajectory for a given change. Therefore, the proposed approach achieves reliable control with accurate tracking of inputs despite the variability in the patients and other disturbances.




(a)




(b)




(c)

***Fig. 4.*** *Comparative analysis of different methodologies.*

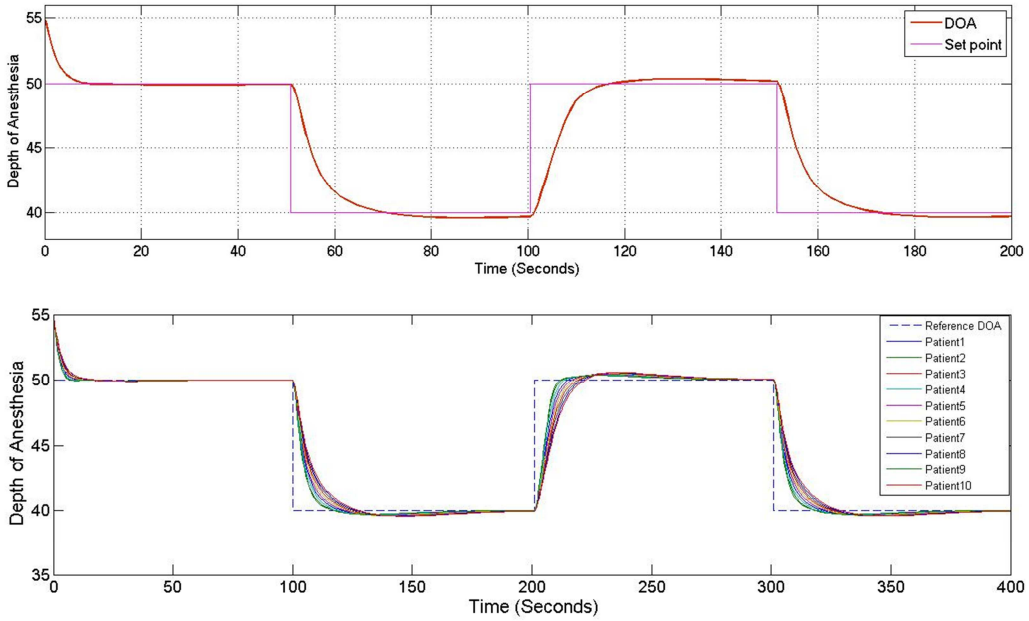



***Fig. 5.*** *Response of the proposed system.*

## 6. Conclusion

The ability of the PID controller to exercise precise control combined with the experts-knowledge-based FIS led to a fast and robust control strategy. The proposed methodology showed reliable control despite the variation from patient to patient and other disturbances. However, the system can be validated only after it is tested in real time and with real patients. The overall results show that this system is ready for such testing. This confirms the usefulness of FIS with PID for controlling the administration of anaesthesia.

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## References

[1] Chang, Jing Jing, et al. "Automation of anaesthesia: a review on multivariable control." *Journal of clinical monitoring and computing* 29.2 (2015): 231-239.

[2] Beck, Carolyn. "Modelling and control of pharmacodynamics." *European Journal of Control* (2015).

[3] Sopasakis, Pantelis, Panagiotis Patrinos, and Haralambos Sarimveis. "Robust model predictive control for optimal continuous drug administration." *Computer methods and programs in biomedicine* 116.3 (2014): 193-204.

[4] Atchabahian, Arthur, and Thomas M. Hemmerling. "Robotic Anesthesia: How is it Going to Change Our Practice?" *Anesthesiology and pain medicine* 4.1 (2014).

[5] Van Heusden, Klaske, et al. "Design and clinical evaluation of robust PID control of propofol anaesthesia in children." Control Systems Technology, IEEE Transactions on 22.2 (2014): 491-501.

[6] K. Bhole, S. Agashe and Ashok Deshpande, "FPGA implementation of type 1 fuzzy inference system for intravenous anaesthesia*", Fuzzy systems (FUZZ), 2013 IEEE international Conference on,* IEEE, 2013.

[7] Hemmerling, T. M., et al. "Evaluation of a novel closed-loop total intravenous anaesthesia drug delivery system: a randomized controlled trial." *British journal of anaesthesia* 110.6 (2013): 1031-1039.

[8] Hemmerling, Thomas M., Fabrizio Cirillo, and Shantale Cyr. *Decision Support Systems in Medicine-Anaesthesia, Critical Care and Intensive Care Medicine*. INTECH Open Access Publisher, 2012.

[9] Hemmerling, T. M., et al. "First robotic tracheal intubations in humans using the Kepler intubation system." *British journal of anaesthesia* 108.6 (2012): 1011-1016.

[10] Jin-Oh Hahn and et. al, "A Direct Dynamic Dose-Response Model of Propofol for Individualized Anaesthesia Care", IEEE transactions on biomedical engineering, vol. 59, no. 2, February 2012, 571-578.

[11] J. Y. Lan and et. al, "Review: intelligent modelling and control in anaesthesia," in Journal of Medical and Biological Engineering, vol. 32, pp. 293–308, 2012.

[12] K. A. Bhole, D. N. Sonawane, S. D. Agashe, Vinayak Desurkar and Ashok Deshpande, "FPGA implementation of Type 1 Fuzzy Inference System for Intravenous Anaesthetic drug delivery", *World conference on soft computing*, 2011.

[13] Hemmerling, Thomas M. *Decision support systems in anaesthesia, emergency medicine and intensive care medicine*. INTECH Open Access Publisher, 2011.

[14] Hemmerling, Thomas M., et al. "Robotic Anesthesia–A Vision for the future of Anesthesia." *Translational Medicine@ Uni Sa* 1 (2011): 1.

[15] Mirza, Mansoor, Hamid Gholam Hosseini, and Michael J. Harrison. "A fuzzy logic-based system for anaesthesia monitoring." *Engineering in Medicine and Biology Society (EMBC), 2010 Annual International Conference of the IEEE*. IEEE, 2010.

[16] Caruso, Antonello LG, and Manfred Morari. "Model predictive control for propofol sedation." *World Congress on Medical Physics and Biomedical Engineering, September 7-12, 2009, Munich, Germany*. Springer Berlin Heidelberg, 2009.

[17] Caruso, Antonello LG, et al. "Control of drug administration during monitored anaesthesia care." *Automation Science and Engineering, IEEE Transactions on*6.2 (2009): 256-264.

[18] Hemmerling, Thomas, et al. "A novel closed-loop system to administer propofol comparison with manual control." *Canadian Journal of Anesthesia*55 (2008): 4738721-4738722.

[19] M. M. S. Anthony Absalom, An Overview of TCI and TIVA. Academia Press, 2008.

[20] Dunsmuir, Dustin, et al. "A knowledge authoring tool for clinical decision support." Journal of clinical monitoring and computing 22.3 (2008): 189-198.

[21] C. Vanlersberghe, and F. Camu, “Propofol”, in Modern Anaesthetics, Springer, 2008, Ch 11, pp. 227-252.

[22] R. D. Miller, Miller's Anaesthesia, 6th ed., e. Lee A Fleisher, Ed. Elsevier, 2005.

[23] Krol, Marina, and David L. Reich. "Development of a decision support system to assist anaesthesiologists in operating room." Journal of medical systems 24.3 (2000): 141-146.

[24] Schnider and et. al, “The influence of age propofol pharmacodynamics," Anaesthesiology, vol. 90, pp. 1502-1516, 1999.

[25] Zadeh, Lotfi A. "Fuzzy logic and approximate reasoning." Synthese 30.3-4 (1975): 407-428.