31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Fuzzy Control for Closed-Loop, Patient-Specific Hypnosis in Intraoperative Patients: A Simulation Study

Brett L. Moore, MS, Larry D. Pyeatt, PhD, and Anthony G. Doufas, MD, PhD

Abstract—**Research has demonstrated the efficacy of closed-loop control of anesthesia using bispectral index (BIS) as the controlled variable, and the recent development of model-based, patient-adaptive systems has considerably improved anesthetic control. To further explore the use of model-based control in anesthesia, we investigated the application of fuzzy control in the delivery of patient-specific propofol-induced hypnosis. In simulated intraoperative patients, the fuzzy controller demonstrated clinically acceptable performance, suggesting that further study is warranted.**

I. Introduction

THE bispectral index (BIS) quantifies the relationship among the electroencephalogram's (EEG) underlying sinusoidal components [1] to provide a validated measure of the hypnotic component of anesthesia[1] [2]. As such, BIS has been used to guide anesthesia in closed-loop control applications [3][4], yielding overall better control, decreased anesthetic consumption, enhanced hemodynamic stability, and faster recovery when compared to manual anesthetic management [4][5].

Historically, the application of proportional-integral-derivative (PID) control [3] in closed-loop anesthesia has demonstrated moderate success. However, successes have been constrained by the limitations of the controlling technique [6], as well as the level of complexity and variability encountered in human physiology [7][8].

A recently developed model-based, patient-adaptive system [9] in which the drug dose-response relationship is continuously updated has demonstrated superior performance when compared to a PID-based technique in a simulation study. However, it has been observed that the efficacy of PID control may be improved by targeting the effect site concentration of propofol, rather than plasma concentration [3].

The objective of this simulation study was to investigate the application of fuzzy control in closed-loop delivery of propofol-induced hypnosis. The application is challenging: the BIS signal is inherently noisy, and a patient's pharmacodynamic response to propofol infusion is known to be non-linear, time-delayed, and subject to inter-patient variability. Motivated in part by the successes reported by Schaublin in mechanical ventilation [10], a similarly challenging application, a fuzzy control method was chosen.

Manuscript received April 23, 2009.

B. L. Moore is a doctoral student with the Texas Tech University Computer Science department, Abilene, TX, 79601 USA (phone: 210-391-7038; e-mail: brett.moore@gmail.com).

L. D. Pyeatt is Associate Chair of the Department of Computer Science, Texas Tech University, Abilene, TX, 79601 USA (e-mail: larry.pyeatt@ttu.edu).

A. G. Doufas is Associate Professor at the Department of Anesthesia, Stanford University School of Medicine, Stanford, CA, 94305 USA. (e-mail: agdoufas@stanford.edu)

[1] Hypnosis is the suppression of cortical activity and is a fundamental component of anesthesia, which also includes analgesia and amnesia.

II. Methods

For this investigation, the controller was developed using basic fuzzy set operations, and optimization was accomplished with simulated annealing. The controller was then applied to a randomly generated population of 1000 simulated intraoperative patients, and control performance was assessed.

A. Fuzzy Controller Architecture

To develop our fuzzy controller, we first identified three input variables for patient state classification, one of which required the inclusion of a model of propofol effect. A structured mechanism for linking propofol infusion rate to patient state was then devised.

1) Controller Inputs

To achieve and maintain a desired level of hypnosis (BIS_{target}), the controller observed the patient's bispectral index ($BIS_{measured}$) on 5s intervals. Since BIS is an inherently noisy signal, $BIS_{measured}$ was smoothed using a recursive "alpha-beta" filter (α=0.85). From these parameters, two control input variables were computed: E and ΔE. E was defined as the difference in $BIS_{measured}$ and BIS_{target}. ΔE was defined as the change in E over 15s, or $E_t - E_{t-2}$. The third input variable, the predicted BIS error, pE relied on general models for propofol response to predict the control error 60s in the future.

2) Propofol Pharmacokinetics and Pharmacodynamics

Propofol pharmacokinetics were modeled using Schnider's three-compartment model [10], which provides the *central*, *rapid*, and *slow* compartments to estimate the time-dependent distribution of propofol. Propofol is introduced into the central compartment, the patient's blood volume, via intravenous infusion. First-order differential equations model the gradient-driven flow of propofol between compartments, and a diffusion constant to model propofol metabolism is also provided. In the Schnider model, these diffusion constants are dependent upon patient height, weight, gender, and age.

An infusion of intravenous propofol exhibits a 2.7 minute time-to-peak effect as measured by BIS [12]. To model this

delay, the Schnider kinetic model was augmented with a fourth compartment, the *effect site* [5]

To model the hypnotic effect of propofol (as measured by BIS), a nonlinear pharmacodynamic model was developed using the observations of Doufas [12]. BIS is a statistically derived measure that lies in the range [0,100] and varies proportionally with consciousness [1]. Using this model, the controller could generally predict propofol effect based on the estimated effect site concentration.

3) Fuzzy Classification of Patient State

In 1965, Zadeh introduced *fuzzy logic*, a system for logical operations on fuzzy sets [13]. In this system, fuzzy set membership is represented as a real number in the range [0, 1], unlike conventional binary-valued set theory. This representation admits a variety of membership functions; of these, we chose Gaussian kernels. To classify an input variable, the kernels were uniformly distributed along each variable's bounded interval, and each kernel was scaled by a standard deviation of 3.

The input variables E and pE were classified using nine kernels spanning the bounded interval [-20,20] BIS. Kernels were centered at the following points: -20, -15, -10, -5, 0, 5, 10, 15, and 20. These kernel placements corresponded to the negative and positive linguistic classifications of Extreme, High, Low, Slight, as well as Zero. Under this scheme, Extreme Negative was designated XN, Zero was designated Z, and Extreme Positive was designated XP. ΔE was classified using three kernels spanning the bounded interval [-5,5] BIS. Kernels were placed at -5, 0, and 5; these kernels corresponded to linguistic classifications of Negative, Zero, and Positive. Kernel placement and linguistic classifications were chosen under the supervision of A.G. Doufas, an Associate Professor of Anesthesia and practicing anesthesiologist.

4) Defuzzification: Determining Propofol Infusion Rate

Given a patient state classification, the next objective was to emulate an experienced anesthetist and match patient state to the required propofol infusion rate for achieving and maintaining the desired hypnotic level. When observing a patient state of $E=19$, $\Delta E=-1$, and $pE=20$ (which would be classified as [XP,Z,XP]), this clinician may reasonably conclude that a bolus of propofol is indicated. Likewise, this clinician may recognize that a classification of [SN,Z,Z] represents an equilibrium state and no infusion is needed. However, this state classification method permits 243 combinations of state variables (9 x 3 x 9), and optimal dosing in many combinations may not be obvious.

To formalize the process of linking patient state to infusion rate, we *defuzzified* patient state by computing the fuzzy set intersection [13]:

$$I(E, \Delta E, pE) = \min\left(M_i(E), M_j(\Delta E), M_k(pE)\right), \quad (1)$$

where i, j, and k iterated over the respective sets of membership kernels. The propofol infusion rate ($ml \cdot min^{-1}$) was then computed as the weighted centroid of I [14]:

$$F(E, \Delta E, pE) = \sum_{i,j,k} I(E, \Delta E, pE)_{i,j,k} \cdot P_{i,j,k} \quad (2)$$

As shown in (2), a weighted sum of the fuzzy set intersections was computed using P, a three-dimensional weighting function that presented a direct method of optimizing infusion rate selection.

B. Policy Optimization

To determine a near-optimal dosing policy for the set of all patient states, the task was structured as a three-dimensional minimization problem and optimized using Simulated Annealing.

1) Simulated Annealing

Simulated Annealing is a global optimization method modeled after the annealing process in metallurgy and is used to find non-local solutions in large state spaces. The method resembles a random walk in its exploration but employs acceptance criteria in a manner that resembles a hill-climbing technique [15].

In this application, optimization began with a randomly selected configuration in which the members of P were selected from [-1.0,1.0] with uniform probability. This policy, P_0, was evaluated for fitness, and exploration of configuration space was initiated with an arbitrary transition to a neighboring state.

A successor configuration S_{t+1} was visited by randomly choosing a three-dimensional step vector ΔP and updating P_t accordingly: $S_{t+1} = P_t + \Delta P$. This successor state was then evaluated for fitness and accepted ($P_{t+1} = S_{t+1}$) if the successor configuration demonstrated improvement. If the successor configuration was not accepted, the configuration remained unchanged, i.e. $P_{t+1} = P_t$.

Although better configurations were always accepted, occasionally the system was permitted to achieve sub-optimal neighboring states to avoid becoming stuck in a locally optimal solution. Following the example of Metropolis [16], we applied a Boltzmann distribution to determine the system *temperature*, the likelihood of accepting non-improving configurations. As optimization progressed, the system was "cooled" proportionally with the number of iterations and non-improving state transitions became less likely.

In this application, the temperature also influenced the rate of exploration. Initially, the step parameter ΔP was constrained to the interval [-0.1,0.1] to encourage global exploration. Over the course of optimization, the step interval was scaled proportionally with temperature to focus optimization. Although good solutions were usually found quickly, optimization was permitted to run for 10^8 iterations, or approximately twenty hours of computation on a contemporary desktop computer.

2) Fitness Criterion

Since "optimality" implies a measure of comparison, we implemented a benchmark control task to grade policy configurations. In this task, the controller guided propofol-induced hypnosis in a simulated intraoperative patient (male, 70 kg, 180 cm, 21 yr) for 60 minutes. The patient was assumed fully conscious at the beginning of the task ($BIS_{measured} \approx 95$), so the controller was challenged with both

induction and maintenance of anesthesia. Propofol infusion rate selections were made on 5s intervals for consistency with commercially-available bispectral index monitors. The infusion rate was bounded to the interval [0,4.0] ml·min^{-1} and discretized to 0.01 ml·min^{-1} to accommodate commercially-available infusion pumps. Control error ($BIS_{measured} - BIS_{target}$) was assessed on 5s intervals. The fitness criterion, root-mean-squared error (RMSE), was computed over the resulting 720 samples.

In practice, a fuzzy logic controller developed in this manner showed signs of target dependence, i.e. a policy developed at BIS_{target}=40 may not yield good performance at BIS_{target}=60. Since both of these targets are clinically useful, two distinct controllers were optimized for these targets; policies for these controllers were labeled P_{40} and P_{60}, respectively.

C. Policy Evaluation and Selection

To evaluate the resulting fuzzy logic controllers, we simulated 1000 episodes of propofol hypnosis, each lasting 240 minutes. BIS targets of 40 and 60 were presented in random order, and the selected target remained in effect for 120 minutes. The active controller (P_{40} or P_{60}) was tasked with achieving and maintaining the desired target. As in the fitness test, control decisions were made on 5s intervals.

For a heterogeneous patient population, each patient's demographic parameters were randomly selected with uniform probability from the associated ranges: age [18,45] years, weight [45,90] kg, and height [150,190] cm. Gender was chosen similarly.

A clinical system for closed-loop hypnosis must be prepared to manage other sources of inter-patient variation, as well. Accordingly, we developed a Patient Variability Model (PVM) to challenge the controller with variation in propofol sensitivity and BIS measurement noise. Fig. 1 illustrates the interaction between the controller and simulated intraoperative patient. As shown, the PVM models patient variation with perturbations of propofol pharmacodynamics (drug effect) without the controller's direct observation (Fig. 1). Equation (3) formalizes the relationship illustrated in Fig. 1.

$$BIS_{measured}(t) = BIS_{ideal}(t) + \Delta BIS_{PVM}(t) \quad (3)$$

Changes in propofol sensitivity, ΔBIS_{PVM}, were modeled as a sum of time-dependent and time-independent parameters:

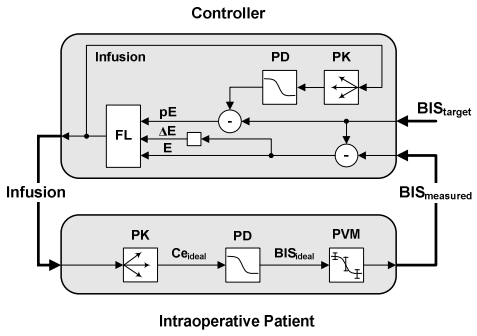

Fig. 1. Interaction between the fuzzy logic controller and the simulated intraoperative patient.

$$\Delta BIS_{PVM}(t) = \kappa_{individual} + \Delta BIS(t) + \varepsilon \,. \quad (4)$$

A static term, $\kappa_{individual}$, chosen randomly from [-10,10] BIS, represented constant deviation in the form of individual sensitivity and persistent surgical stimulus [7]. BIS measurement noise, ε, was modeled as a stationary, normally-distributed signal with mean zero and standard deviation three [9].

A non-stationary perturbation $\Delta BIS(t)$ was also modeled. In its positive form (chosen with p=0.8), this component represented the arousing effect of a noxious surgical stimulus [8]. In the negative form (chosen with p=0.2), this component represented the depression of BIS associated with synergistic drug interaction.

Since the bispectral index is a time-averaged parameter, non-stationary perturbations cannot be observed as abrupt signal changes. Accordingly, we modeled $\Delta BIS(t)$ by passing a square function through a recursive "alpha-beta" filter, which yielded a smooth, lagging curve. To challenge the controller with a range of clinically relative disturbances, the peak magnitude of the square function was randomly chosen [1,20] BIS, and duration was chosen from [2,10] min. The interval between successive impulses was chosen from [4,20] min.

D. Performance Analysis

Analysis of steady-state control performance followed the methods of Varvel [17] by computing the Performance Error (PE) for all timesteps in each hypnotic episode:

$$PE(t) = \frac{BIS_{measured}(t) - BIS_{target}(t)}{BIS_{target}(t)} \times 100 \quad (5)$$

From this parameter, the median PE (MDPE), median absolute PE (MDAPE), wobble, and divergence values were computed over the population of 1000 patients. MDPE measured control bias, MDAPE served as a measure of control accuracy, wobble measured the intra-subject variability, and divergence indicated the stability of control.

Additionally, we computed the Controlled metric, which was defined as the percentage of timesteps $BIS_{measured}$ was within ±5 of BIS_{target}.

III. Results

Table 1 summarizes the observed results.

TABLE I
OBSERVED PERFORMANCE PARAMETERS

Parameter	Observation mean (95% CI)	
MDPE (%)	-0.32	(-0.36, -0.28)
MDAPE (%)	2.52	(2.49, 2.54)
Wobble (%)	2.50	(2.48, 2.53)
Divergence (%·hr^{-1})	0.002	(0.002, 0.002)
Controlled (%)	89.9	(89.6, 90.1)

MDPE is median performance error, and MDAPE is median absolute performance error.

IV. Discussion

The results in Table1 indicate that the fuzzy controller provided accurate and stable control for the selected BIS targets. The control bias was less than 1%, and the control accuracy was approximately 2.5 %. The small wobble and divergence values, 2.5% and 0.002 %·hr $^{-1}$, respectively indicate that stable control was achieved – despite the destabilizing influence of the Patient Variation Model. This degree of control is also reflected in the high Controlled measure.

These results compare favorably with the closed-loop hypnosis simulation study reported by Struys [9] in which a model-based controller was compared to conventional PID control. Likewise, the results compare well with the work of De Smet [18]. In that study, the authors conclude that an MDPE of -7.8%, an MDAPE of 11.5%, a wobble value of 8.4%, and near-zero divergence was indicative of good control. Although we can make no direct comparison between our control performance and the performances reported by Struys and De Smet, we may borrow their criteria for good control and conclude that the fuzzy controller provided accurate and stable control.

The principle limitation of this study was the fidelity of the Patient Variability Model (PVM). We developed the PVM using published data [7][8] and our own clinical observations. We believe the PVM models intraoperative patient variation more accurately than other reported systems and challenges control in a clinically relevant manner. However, we lack evidence correlating the PVM with actual clinical observations.

V. Conclusions

This simulation study suggests that fuzzy control, when developed and applied as described, may be suitable for closed-loop delivery of propofol hypnosis in the clinical setting. Our PVM challenged the controller with credible instances of patient variation, yet the controller demonstrated accurate and stable hypnosis. Based upon these results, we consider a well-controlled healthy human volunteer investigation as a reasonable next step in the study of closed-loop fuzzy control of anesthesia.

References

[1] I. Rampil, "A primer for EEG signal processing in anesthesia," *Anesthesiology,* 1989, vol. 89, pp. 980–1002.

[2] P. Sebel , E. Lang, I. Rampil, P. White, R. Cork, M. Jopling, N. Smith, P. Glass, and P. Manberg, "A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect," *Anesth. Analg.*, 1997, vol. 84, pp. 891–21.

[3] A. Absalom and G. Kenny, "Closed-loop control of propofol anaesthesia using bispectral index: performance assessment in patients receiving computer-controlled propofol and manually controlled remifentanil infusions for minor surgery," *Br. J. Anaesth.*, 2003, vol. 90, pp. 737–41.

[4] N. Liu, T. Chazot, A Genty, A. Landais, A. Restoux, K. McGee, P. Laloe, B. Trillat, L. Barvais, and M. Fischler, "Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: closed-loop versus manual control: a prospective, randomized, multicenter study," *Anesthesiology,* 2006, vol. 104, pp. 686–95.

[5] M. Struys, T. De Smet, L. Versichelen, S. Van De Velde, R. Van den Broecke, and E. Mortier, "Comparison of closed-loop controlled administration of propofol using Bispectral Index as the controlled variable versus 'standard practice' controlled administration,", *Anesthesiology,* 2001, vol. 95, pp. 6–17.

[6] K. Olkkola, H. Schwilden, and C. Apffelstaedt, "Model-based adaptive closed-loop feedback control of atracurium-induced neuromuscular blockade," *Acta Anaesthesiol. Scand.*, 1991, vol. 35, pp. 420–3.

[7] M. Wood, "Variability of human drug response," *Anesthesiology,* 1989, vol. 71, pp. 631–4.

[8] H. Ropcke, B. Rehberg, M. Koenen-Bergmann, T. Bouillon, J. Bruhn, and A.Hoeft, "Surgical stimulation shifts EEG concentration-response relationship of desflurane", *Anesthesiology,* 2001, vol. 94, pp. 390–9.

[9] M. Struys, T. De Smet, S. Greenwald, A. Absalom, S. Binge, and E. Mortier, "Performance evaluation of two published closed-loop control systems using bispectral index monitoring: a simulation study," *Anesthesiology,* 2004, vol. 100, pp. 640–7.

[10] J. Schaublin, M. Derighetti, P. Feigenwinter, S. Petersen-Felix and A. Zbinden, "Fuzzy logic control of mechanical ventilation during anaesthesia," *Br. J. Anaesth.*, 1996, vol. 77, pp. 636–41.

[11] T. Schnider, C. Minto, P. Gambus, C. Andresen, D .Goodale, S. Shafer, and E. Youngs, "The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers," *Anesthesiology,* 1998, vol. 88, pp. 1170–82.

[12] A. Doufas, M. Bakhshandeh, A. Bjorksten, S. Shafer, and D. Sessler, "Induction speed is not a determinant of propofol pharmacodynamics," *Anesthesiology,* 2004, vol. 101, pp. 1112–21.

[13] L. Zadeh, "Fuzzy sets", *Information and Control*, 1965, vol. 8, pp. 383–53.

[14] G. Gerla, "Fuzzy logic: Mathematical Tools for Approximate Reasoning," 2000, Kluwer Academic Publishers, Dordrect, The Netherlands.

[15] S. Kirkpatrick and C. Gelatt, Jr. and M. Vecchi, "Optimization by Simulated Annealing," *Science*, 1983, vol. 220, pp. 671–80.

[16] N. Metropolis, A. Rosenbluth, M. Rosenbluth, A. Teller, and E. Teller. "Equations of State Calculations by Fast Computing Machines," *Journal of Chemical Physics*, 1953, vol. 21, pp. 1087–92.

[17] J. Varvel, D. Donoho, and S. Shafer, "Measuring the predictive performance of computer-controlled infusion pumps," *J. Pharmacokinet. Biopharm.*, 1992, vol 20. pp. 63–94.

[18] T. De Smet, M. Struys, S. Greenwald, E. Mortier, and S. Shafer, "Estimation of optimal modeling weights for a Bayesian-based closed-loop system for propofol administration using the bispectral index as a controlled variable: a simulation study," *Anesth. Analg.*, 2007, vol. 105, pp. 1629–38.