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Hypnosis control based on the minimum concentration of anesthetic drug for maintaining appropriate hypnosis*

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***Abstract*— This paper proposes a novel hypnosis control method using Auditory Evoked Potential Index (aepEX) as a hypnosis index. In order to avoid side effects of an anesthetic drug, it is desirable to reduce the amount of an anesthetic drug during surgery. For this purpose many studies of hypnosis control systems have been done. Most of them use Bispectral Index (BIS), another hypnosis index, but it has problems of dependence on anesthetic drugs and nonsmooth change near some particular values. On the other hand, aepEX has an ability of clear distinction between patient consciousness and unconsciousness and independence of anesthetic drugs. The control method proposed in this paper consists of two elements: estimating the minimum effect-site concentration for maintaining appropriate hypnosis and adjusting infusion rate of an anesthetic drug, propofol, using model predictive control. The minimum effect-site concentration is estimated utilizing the property of aepEX pharmacodynamics. The infusion rate of propofol is adjusted so that effect-site concentration of propofol may be kept near and always above the minimum effect-site concentration. Simulation results of hypnosis control using the proposed method show that the minimum concentration can be estimated appropriately and that the proposed control method can maintain hypnosis adequately and reduce the total infusion amount of propofol.**

I. Introduction

In order to avoid side effects of an anesthetic drug such as postoperative nausea and vomiting, it is desirable to reduce the amount of an anesthetic drug for making patients unconscious during surgery. However, to adjust infusion rate of an anesthetic drug for always maintaining an appropriate hypnosis level of patients is a heavy burden to anesthesiologists. To realize desirable hypnosis control during surgery without increasing anesthesiologists' burden, many studies of automatic hypnosis control systems have been done [1]–[7]. Most of them use Bispectral Index (BIS) [8] as a hypnosis index, while BIS has problems of dependence on anesthetic drugs and nonsmooth change near some particular values [9], [10].

On the other hand, Auditory Evoked Potential Index (aepEX), another hypnosis index calculated as the sum of the square roots of the absolute differences between successive 0.56 ms segments of the auditory evoked potential waveform to 6.9 Hz auditory stimulation, has attracted attention due to its ability of clear distinction between patient consciousness and unconsciousness during surgery and comparative independence of anesthetic drugs [9], [11], although its instability might be considered in some situations. An automatic control system using aepEX as a hypnosis index has already been developed [2], however it adjusts the infusion rate of an anesthetic drug so as to keep the aepEX value at a set-point and has drawbacks of taking long time for anesthesia induction and excessive sensitivity to measured noises and disturbances.

In this paper, we propose a new hypnosis control method utilizing the property of aepEX. It consists of an estimation method of the minimum effect-site concentration of an anesthetic drug for keeping unconsciousness utilizing the relation between the effect-site concentration and aepEX, and a hypnosis control method that adjusts the infusion rate of an anesthetic drug to keep the effect-site concentration near and always above the minimum concentration. Using this control method, reduction of total infusion amount of an anesthetic drug can be expected.

This paper is organized as follows. The idea of the proposed control method is given in Section II. The model used for the estimation of the minimum effect-site concentration and hypnosis control is shown in Section III. The proposed estimation and control methods are given in detail in Section IV, and the simulation results are shown in Section V. Discussion on the proposed method is made in Section VI.

II. Basic idea of proposed control method

In this section, we give the basic idea of the proposed hypnosis control method.

Fig. 1 shows the relation between effect-site concentration of propofol, an anesthetic drug, and aepEX measured from a patient after anesthesia induction. The effect-site concentration of propofol is estimated from clinical data of propofol infusion rate based on a pharmacokinetic (PK) model. The figure shows that aepEX is little changed in the range of sufficient hypnosis (the shaded region), while it rapidly increases near awakening. Thus, appropriate hypnosis can be maintained by keeping the effect-site concentration of propofol within the shaded region, i.e. above the concentration corresponding to the left boundary of the region. This effect-site concentration is the minimum effect-site concentration for keeping appropriate hypnosis (denoted by $c_{\mathrm{e,min}}$ in the following). Thus, desirable hypnosis control can be achieved by 1) estimating the minimum effect-site concentration $c_{\mathrm{e,min}}$ for keeping hypnosis at an appropriate

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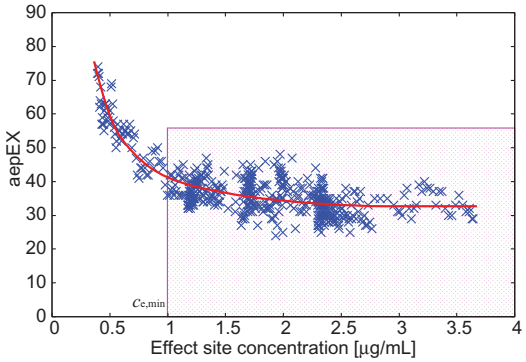


Fig. 1. Relation between estimated effect-site propofol concentration based on the pharmacokinetic model given by Barr et al. [16] and measured aepEX.

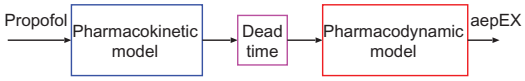


Fig. 2. Model of hypnosis response to propofol infusion.

level, and 2) maintaining the effect-site concentration near and always above $c_{\mathrm{e,min}}$.

We give the detailed estimation and control method proposed in this paper in the following sections.

III. Model of Hypnosis Response to Anesthetic Drug

To construct an effective control system using the proposed method, we must accurately estimate the minimum effect-site concentration $c_{\mathrm{e,min}}$ of propofol for keeping appropriate hypnosis level. Therefore, a suitable model of hypnosis response to propofol for this purpose is necessary. In this section, we give the structure of the model of aepEX response to propofol infusion, and select a desirable model among the existing models.

The hypnosis response to propofol can be modeled as series connection of a pharmacokinetic (PK) model representing change of propofol concentrations in a human body, a pharmacodynamic (PD) model representing relationship between effect-site propofol concentration and hypnosis level, and dead time due to movement of propofol in an intravenous fluid line, distribution of propofol in blood vessels, and calculation time of aepEX, as shown in Fig. 2.

Many parameter sets have been proposed for the propofol pharmacokinetics [12]–[16]. Since we use the effect-site propofol concentration calculated from a PK model to distinguish between consciousness and unconsciousness, the model parameters that give the highest accuracy of the distinction are desirable. Thus, we examined the accuracy of distinction between consciousness and unconsciousness for the existing model parameter sets based on clinical data of 13 patients (57.3 ± 11.4 years, 58.2 ± 8.8 kg (mean $\pm$ standard deviation)) measured at Kagawa University Hospital. The accuracy of each model parameter set is evaluated as follows. First, the period in which a patient is possibly conscious, i.e. the period of body movement and later than dead time after stopping propofol infusion, is defined as "conscious period" and the period other than the conscious period is defined as "unconscious period." Also, $c_{\mathrm{u,min}}$ is defined as the minimum effect-site concentration of propofol during the unconscious period, and $c_{\mathrm{c,max}}$ is defined as the maximum effect-site concentration of propofol during the conscious period. We consider the following two classification conditions:

- **Condition 1**: If the current concentration c satisfies $c < c_{\mathrm{u,min}}$ or $\mathrm{aepEX} > 56$, the patient can be considered to be conscious.
- **Condition 2**: If c satisfies $c > c_{\mathrm{c,max}}$ and $\mathrm{aepEX} < 56$, the patient can be considered to be unconscious.

The accuracy of the model can be evaluated by

- the probability of misclassification by Condition 1 when patients are unconscious, and
- the probability of misclassification by Condition 2 when patients are conscious.

Comparing the probabilities using representative PK models given in [12]–[16], the PK parameters given by Barr et al. [16] has the highest accuracy (misclassification probabilities are 6.4% and 3.0%, respectively). The effect-site propofol concentration in Fig. 1 is calculated using the Barr PK model parameters, and the thick solid red curve is an approximated PD model.

IV. Proposed Estimation Method of Minimum Effect-Site Propofol Concentration and Control Method

As shown in Section II, the minimum effect-site concentration $c_{\mathrm{e,min}}$ can be determined by finding the concentration at which the change rate of aepEX to effect-site concentration becomes large. However, $c_{\mathrm{e,min}}$ of each patient is different and time-varying. In this section, we propose an estimation method of $c_{\mathrm{e,min}}$ for keeping appropriate hypnosis and a control method based on the estimated minimum concentration.

A. Estimation method of the minimum effect-site concentration in the induction period

Since steady aepEX measurement is not always possible in the anesthesia induction period, we use BIS for estimation of the initial minimum concentration if BIS is measured. First, we give an estimation method of the minimum concentration from the measured BIS. From the clinical data of the 13 patients of the cases where anesthesia is induced by propofol bolus of 2 mg/kg followed by continuous infusion of 10 mg/kg/h, we identified PD models for aepEX and BIS as sigmoid $E_{\max}$ models respectively, and $c_{\mathrm{e,min}}$ of each patient. From them the relation between BIS and aepEX is calculated and the BIS value corresponding to $c_{\mathrm{e,min}}$ is obtained. From the obtained results $c_{\mathrm{e,min}}$ can be estimated by

$$c_{\mathrm{e,min}} = 0.047 c_{\mathrm{BIS,45}} + 0.87 \mu\mathrm{g/mL} \tag{1}$$

where $c_{\mathrm{BIS,45}}$ is the propofol concentration at which the BIS value decreases 45% of the maximal effect intensity of BIS from the initial value.

If only the aepEX value can be used, we estimate the minimum concentration from the measured aepEX. From the

clinical data of the 13 patients we determined the estimation method of the initial minimum concentration as follows. If the measured aepEX becomes lower than 37 in the first 10 minutes, the initial minimum concentration is determined as the concentration corresponding to $\mathrm{aepEX} = 37$ of the PD model identified from the first 10 minutes. If the measured aepEX does not become lower than 37, the initial minimum concentration is determined as the concentration at which the aepEX value decreases 90% of the maximal effect intensity of aepEX.

B. Estimation method of the minimum effect-site concentration in the control period

Now, we give the estimation method of the minimum concentration in the control period. When hypnosis is kept at a sufficiently deep level, the propofol concentration might be too high. To avoid too high concentration of propofol, the minimum concentration is periodically reestimated. Reestimation method is as follows. When hypnosis is kept at a suffciently deep level for 15 minutes, the target concentration is decreasing at the rate of $1/(0.75T_L + 180\mathrm{s})$, where T_L is the dead time identified from the data of the first 10 minutes. Then we calculate $\mathrm{aepEX}_{\mathrm{slope}}$, the slope of PD model for aepEX within the range of $[c, c+0.5\,\mu\mathrm{g/mL}]$ (c is the current concentration) from data for the last 15 minutes, and $\overline{\mathrm{aepEX}}_1$ and $\overline{\mathrm{aepEX}}_2$, the averaged aepEX values within the range of effect-site concentration of $[c, c+0.5\,\mu\mathrm{g/mL}]$ and $[c+0.5\,\mu\mathrm{g/mL}, \infty]$, respectively. The minimum concentration is determined as $c_{\mathrm{e,min}} = c$ when these values satisfy the conditions:

$$\mathrm{aepEX}_{\mathrm{slope}} < -5\,\mathrm{mL}/\mu\mathrm{g}, \tag{2}$$

$$\overline{\mathrm{aepEX}}_1 > \overline{\mathrm{aepEX}}_2, \tag{3}$$

These conditions mean that aepEX steeply changes at c and the averaged aepEX near c is larger than the averaged aepEX corresponding to the concentration above $c + 0.5\,\mu\mathrm{g/mL}$ regardless of measurement noise. If the obtained minimum concentration is very close to that of the last estimation, the estimation procedure is not performed for 90 minutes.

Next, we consider the case where hypnosis is not kept at a sufficiently deep level. If hypnosis level is not sufficient but acceptable, the minimum concentration can be estimated by the estimation method for the sufficient hypnosis case. If hypnosis level is not acceptable, e.g. aepEX becomes larger than 56, hypnosis may be inappropriate and the minimum concentration is determined by

$$c_{\mathrm{e,min}} = c + 0.2\,\mu\mathrm{g/mL},$$

and then the infusion rate of propofol increases immediately.

C. Hypnosis control method

Here, we give a concrete explanation of our hypnosis control method using the estimated minimum concentration. The target r of effect-site propofol concentration is set as $r = c_{\mathrm{e,min}} + 0.3\,\mu\mathrm{g/mL}$ to keep hypnosis at an appropriate level against disturbances such as operative stress. Moreover, we consider constraints that the effect-site propofol concentration $y(t)$ is always kept above the minimum concentration and that the propofol infusion rate $u(t)$ is not over the maximal allowable rate $u_{\max}$, that is

$$y(t) \geq c_{\mathrm{e,min}}, \tag{4}$$

$$0 \leq u(t) \leq u_{\max}. \tag{5}$$

Here, $u_{\max}$ is set to 30 mg/kg/h. It should be noted that the constraint (4) is omitted when the estimation procedure is performed (i.e. the target concentration is decreasing at the given rate).

We choose model predictive control [17] as a control method because we need to handle the above constraints and dead time T_L of the system. We design a model predictive controller for a patient model with the averaged parameters (weight $= 58.2\,\mathrm{kg}$, LBM $= 46.5$, $T_L = 130\,\mathrm{s}$, and $c_{\mathrm{e,min}} = 1.0\,\mu\mathrm{g/mL}$) obtained from the 13 patients. The sampling period is set to 10 seconds, the reference trajectory y_{r} is set to the exponential curve with 5% settling time of 10 minutes, the prediction period is set to $[T_L, T_L + 300\,\mathrm{s}]$, the control horizon is set to 1, and the performance index is set to

$$J = e^{\mathrm{T}}Qe + u^{\mathrm{T}}Ru + \Delta u^{\mathrm{T}}S\Delta u, \tag{6}$$

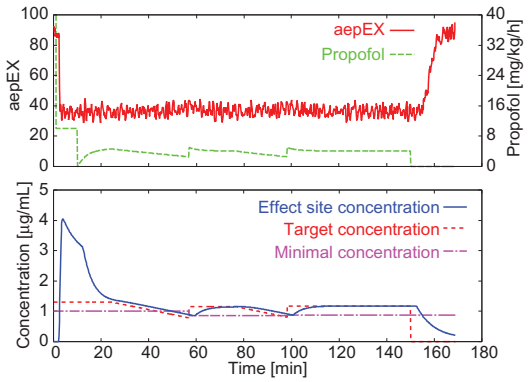
where e is the error between predicted concentration and the reference trajectory, Δu is the variation of infusion rate, Q, R, and S are weights for the error e, the infusion rate u, and the variation of the infusion rate Δu, respectively, and set as $Q = 1\,\mathrm{mg}^{-2}\mathrm{kg}^2\mathrm{h}^2$, $R = 0.05\,\mu\mathrm{g}^{-2}\mathrm{mL}^2$, and $S = 0.02\,\mu\mathrm{g}^{-2}\mathrm{mL}^2$ by trial and error.

V. Simulation

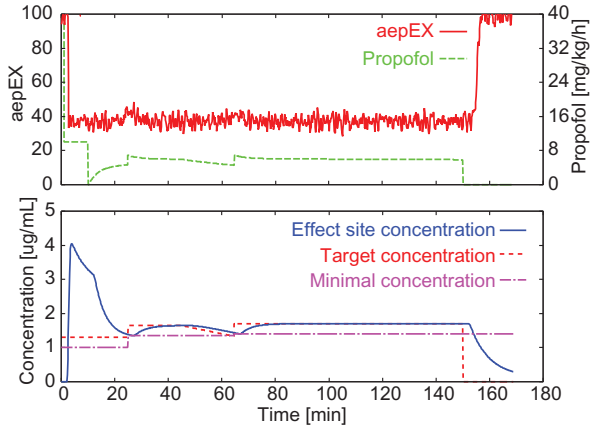
To evaluate the effectiveness of the proposed method of the minimum concentration estimation and hypnosis control, we made simulations. Anesthesia is induced at time 0 by propofol bolus of 2 mg/kg followed by continuous infusion of 10 mg/kg/h. Model predictive control starts at 10 min and keeps hypnosis till 150 minutes. Uniform random noise of up to 7 is added to the measured aepEX data. We do simulation for the nominal patient model and models with identified parameters of the 13 patients. Simulation results for the nominal patient model and a patient model with a high minimum concentration are shown in Fig. 3. Upper figure shows aepEX and propofol infusion rate and lower figure shows the estimated effect-site concentration, the target concentration and minimum concentration estimated by the proposed method. The minimum concentration can be estimated accurately enough, and hypnosis can be kept at the respective desired level. For estimating the minimum concentration aepEX becomes a little bit higher but it may have little influence on hypnosis. The averaged effect-site concentration during keeping hypnosis of the proposed system is $1.39 \pm 0.33\,\mu\mathrm{g/mL}$ and about 9 percent less than that of the clinical data ($1.53 \pm 0.26\,\mu\mathrm{g/mL}$).

VI. Discussion

We propose an estimation method of minimum effect-site concentration of propofol for keeping suffucient hypnosis



(a) Nominal patient



(b) Patient with modeling error of PD parameters

Fig. 3. Simulation results

utilizing the relation between the effect-site concentration and aepEX. The minimum concentration is expected to be obtained accurately using aepEX because the aepEX value is steeply changed near the minimum concentration. The simulation results show that the obtained minimum concentration is appropriate. The obtained minimum concentration can be used not only for our hypnosis control system but also as a target concentration of Target Controlled Infusion (TCI) systems [18]. The proposed method may be effective, while conditions for estimating the minimum concentration must be improved based on more clinical data. Furthermore, an appropriate noise filter may be necessary although measurement noise has little influence on the estimation result in simulation.

We use PK parameters given by Barr et al. because they give the highest accuracy of distinction between consciousness and unconsciousness. However, the accuracy for Marsh [12] and Schnider PK parameters [14] is close to that for Barr parameters. We should compare the estimation and control performance using Barr parameters with that using others.

We also propose a hypnosis control method using the obtained minimum concentration. The simulation results show that the proposed method can keep hypnosis at a sufficiently deep level. Furthermore, since the effect-site concentration is kept near the minimum concentration by the proposed control method, the averaged effect-site concentration can be decreased, that is, the infusion amount of propofol can be reduced compared with the clinical data. There are many studies of hypnosis control methods [1]–[7], which keep a hypnosis index such as BIS at a given target level corresponding to appropriate hypnosis. On the other hand, the proposed method keeps the effect-site concentration of an anesthetic drug in an appropriate range corresponding to sufficient hypnosis, and may fit the usual anesthesia method. We will compare effectiveness of our control method and aepEX with the existing methods and indices based on clinical data.

Of course, hypnosis is only one of the patient states during surgery, other important state such as blood pressure, heart rate, must be kept appropriately. In order to prevent patients to fall in a dangerous state, a risk control mechanism should be added to the control system.

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