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Modeling Anesthetic Drugs' Pharmacodynamic Interaction on the Bispectral Index of the EEG: the Influence of Heart Rate

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Abstract— **The effect of drugs' interaction on the brain signal Bispectral Index (BIS) is of great importance for an anesthesia control drug infusion system. In this study, the objective was to inspect the influence of patient's heart rate on the effect of the drugs on BIS. With this goal, the patient's heart rate was incorporated in an drug interaction model. The model was fitted per patient during anesthesia induction, and tested for prediction under surgery. The results showed that the model with time changing parameters incorporating patient's heart rate has a better performance than a non adjusted model. Three clusters of models were also identified using the fuzzy c-means algorithm. These clusters will help to distinguish between different patients' dynamics.**

I. INTRODUCTION

Anesthesia can be defined as the lack of response and recall to noxious stimuli, involving the use of three drugs, a muscle relaxant, an anesthetic (hypnotic) and an analgesic. The analgesic drug is of great importance since it affects the pharmacodynamics of the anesthetic drug and there is no clear indicator of the degree of pain. The analgesic and anesthetic drugs are interconnected, since they interact with each other so as to achieve an adequate level of depth of anesthesia (DOA) and analgesia [1].

The bispectral index of the EEG (BIS) is a numerical processed, clinically-validated EEG parameter, used as an indicator of the level of DOA, measuring the degree of depression in the central nervous system. The BIS is a number between 0 and 100, where values near 100 represent an "awake" clinical state while 0 denotes the maximal EEG effect possible (i.e., an isoelectric EEG) [2]. Overall, general anesthesia consists of both loss of consciousness through the action of anesthetic drugs, and the inhibition of noxious stimuli reaching the brain through the acting of the analgesics. The intravenous anesthetic drug propofol is used in combination with the analgesic remifentanil.

Propofol and remifentanil have a synergistic relationship. The effect of the combination of these two drugs is greater than that expected as based on the concentration-effect relationships of the individual agents [3]. A model for anesthetic drug interactions can prove to be very useful in understanding the full relationship between the concentrations of the two drugs and drug effects. This model should take into consideration the interactions between drugs and variability between patients.

In a previous study [4], an interaction model [5] was fitted to the data of each patient in the induction phase (first 15 min). The individual patient models were then used to predict BIS during maintenance of anesthesia (surgery), considering the drugs' concentrations. This was a comparative study performed on a wide group of patients to evaluate the influence of the propofol pharmacokinetic model on the overall performance of the interaction model and its prediction ability.

In more recent works [6] [7], a strong correlation was found between the patient heart rate and the amount of propofol needed to produce loss of consciousness, and a relation which the remifentanil concentration. In this study, the objective was to inspect the influence of patient's heart rate on the effect of the drugs on BIS. With this goal, the patient's heart rate was incorporated in the interaction model, allowing for time changing parameters.

The clinical data, the pharmacokinetic (PK) models for propofol and remifentanil are presented in section II. Section III describes the interaction model [5] for the concentration-effect relationship on BIS, while section IV presents the results on the data. Sections V presents the conclusions.

II. CLINICAL DATA

Data collected during 45 neurosurgical interventions were used in this study. All 45 patients were subject to general anesthesia using propofol and remifentanil. The level of unconsciousness (DOA) was manually controlled by the anesthesiologist using as reference the patient's vital signs and BIS. The following data were recorded during the surgery every 5 seconds: BIS, infusion rate of propofol and remifentanil. The infusion rates were used to calculate the plasma and effect concentration of both drugs, as described in the following subsections. The patients studied were 51 ± 16 years, 70 ± 13 kg, 163 ± 9 cm, 28 female. Anesthesia started with a constant infusion 200 ml/hr of propofol until loss of consciousness (LOC), thereafter propofol was changed according to the BIS value. The remifentanil infusion started at LOC.

A. Pharmacokinetic (PK) Models

The PK models of the two drugs use a 3-compartment structure (Fig. 1). For propofol, the parameters from Marsh

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[8] were used, whereas for remifentanil, the parameters from Minto [9] were used. PK model for remifentanil has its parameters adjusted to age, gender, weight and height of the patients, whereas PK model for propofol only takes into consideration the patient's weight. The effect-site compartment

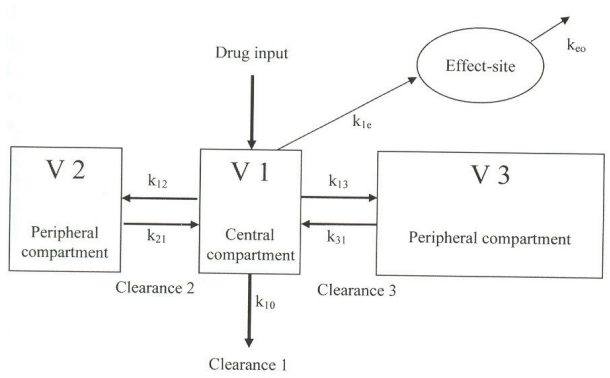


Fig. 1. Compartment pharmacokinetic model. The plasma concentration is defined as the concentration in the central compartment. The effect-site concentration is defined as the concentration in the effect-site. The constants $k_{10}, k_{12}, k_{21}, k_{13}, k_{31}, k_{1e}, k_{e0}$ are microrate constants.

is a hypothetical compartment describing the delay between the plasma concentration and the effect-site concentration. Fig. 1 shows the diagram of the effect-site compartment relationship.

III. BISPECTRAL INDEX (BIS) INTERACTION MODEL

The objective is to describe the relationship between the drugs effect-site concentrations and their effect (BIS). Fig. 2 shows the block diagram of the BIS model.

Bruhn et al. [5] used an interaction model to relate the electroencephalographic parameter values to the effect-site concentrations of propofol and remifentanil.

First, the concentrations were normalized to their respective potencies (EC_{50p} and EC_{50r} for propofol and remifentanil, respectively), i.e. the effect-site concentration at half the maximal effect:

$$U_{remi}(t) = \frac{Ce_r(t)}{EC_{50r}} \qquad U_{prop}(t) = \frac{Ce_p(t)}{EC_{50p}}, \tag{1}$$

where Ce_r and Ce_p are the respective effect-site concentrations of remifentanil and propofol. For an additive interaction, the "effective" concentration is considered to be the sum of the individual concentrations normalized, so the effect ($BIS(t)$, can be described as

$$BIS(t) = BIS_0 \left(1 - \frac{U_{prop}(t) + U_{remi}(t)}{1 + U_{prop}(t) + U_{remi}(t)}\right), \tag{2}$$

where BIS_0 is the effect at zero concentrations (e.g. $BIS_0 =$ 97.7 - monitor restriction). Deviation from a purely additive interaction is modeled by changing the potency of the drug mixture depending on the ratio of the interacting drugs:

$$\phi = \frac{U_{prop}(t)}{U_{prop}(t) + U_{remi}(t)}. \tag{3}$$

By definition, ϕ ranges from 0 (remifentanil only) to 1 (propofol only). Thus, the concentration-response relationship for any ratio of the two drugs regardless of the type of interaction can be described as (4)

$$BIS(t) = BIS_0(1 - \frac{\left(\left(U_{prop}(t) + U_{remi}(t)\right)/U_{50(\phi)}\right)^{\gamma}}{1 + \left(\left(U_{prop}(t) + U_{remi}(t)\right)/U_{50(\phi)}\right)^{\gamma}}) \tag{4}$$

where γ is the steepness of the concentration-response relation, and $U_{50}(\phi)$ is the number of units associated with 50% of maximum effect at ratio ϕ. According to [5], (3) can be simplified to the following quadratic polynomial:

$$U_{50(\phi)} = 1 - \beta_{2,U50}\phi + \beta_{2,U50}\phi^2. \tag{5}$$

The clinical data of these 45 neurosurgeries were used in a previous study [4] to test this model structure. The model parameters were adjusted to the individual patients during the first 15 minutes of induction of anesthesia, and used to predict the BIS signal during surgery. The model results were validated for the 45 cases, using the real propofol and remifentanil doses (ml/h). In this study the objective is to inspect the influence of patient heart rate (HR) on the effect of the drug's on BIS. With that purpose, the propofol potency EC_{50p} was dynamically changed based on the patient's heart rate measured during surgery.

$$EC_{50p}(t) = EC_p * log(HR(t)) \tag{6}$$

IV. RESULTS

The model was fitted to the data of the 45 patients in the induction phase of anesthesia (first 15 min). The interaction model parameters were fitted using nonlinear least squares with the software MATLAB 7.0. The BIS signal was prefiltered with a lowpass second order Butterworth filter. For the interaction model, the parameters EC_p, EC_{50r}, γ and $\beta_{2,U50}$ were obtained for each patient. The mean absolute error was calculated for the results of the model for each patient. Fig. 3 shows the BIS trends for the 45 patients during the induction phase. Fig. 4 shows the effect-site concentrations of propofol and remifentanil.

Fig. 5 shows the modeled BIS value for the 45 patients in the induction (optimization/identification) phase. The mean absolute errors (MAE) for the induction of anesthesia (fitting/identification phase) was 3.87 ± 1.42, 40 patients models had statistical zero errors ($t-test$, $P < 0.05$). The MAE in the maintenance phase (from 15 min until the end of surgery - prediction results) was 13.04 ± 8.22, only one model had statistical zero prediction error ($t-test$, $P < 0.05$). Fig. 6 and Fig. 7 show the modeled BIS signal for patient 18 and 32, in the prediction phase the MAE was 6.23 and 7.08, respectively. Fig. 8 shows the model results for patient model 26 (prediction MAE of 7.73) and the heart rate signal. One can observe the influence of heart rate on the BIS signal, with positive correlation. The higher the heart rate the higher the BIS value, and therefore the smaller the potency

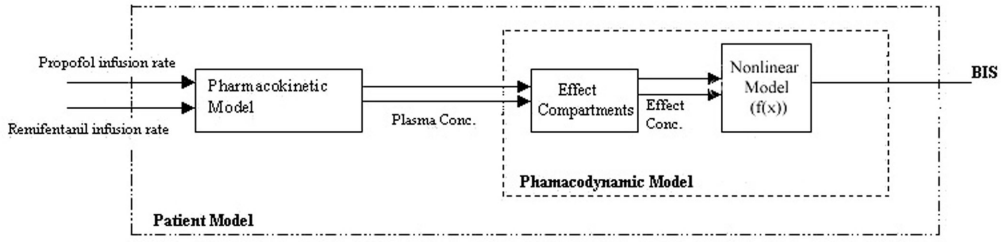


Fig. 2. Block diagram of Bispectral Index (BIS) model, considering the infusion of the anesthetic drug propofol and the analgesic remifentanil.

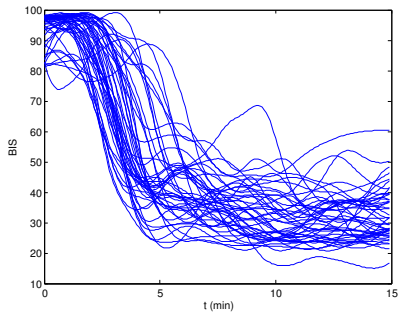
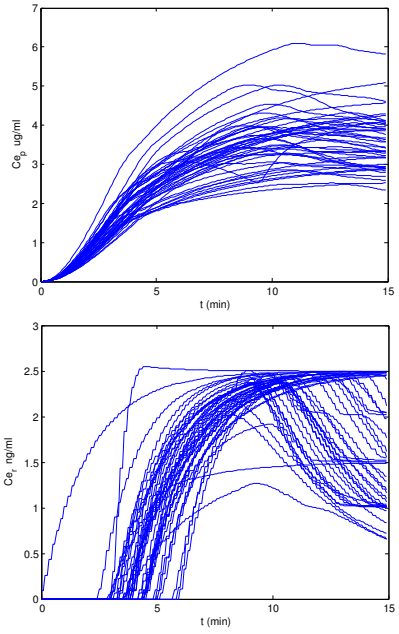


Fig. 3. Recorded BIS values of the 45 patients during the induction phase, i.e. the first 15 min.



A

B

Fig. 4. **A**- Propofol effect-site concentration (Ce_p) and **B**- Remifentanil effect-site concentration (Ce_r) for the 45 patients during the induction phase (i.e. the first 15 min).

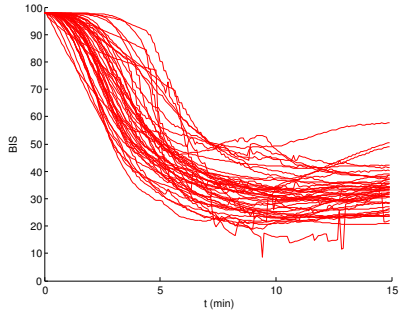


Fig. 5. Modeled BIS values of the 45 patients during the induction phase, i.e. the first 15 min.

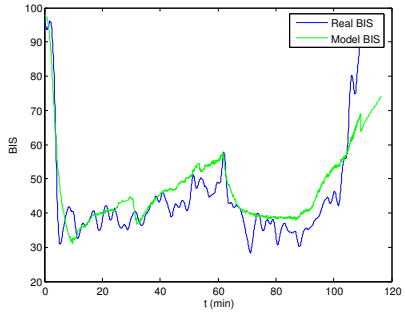


Fig. 6. Real (blue line) versus modeled (green line) BIS values for patient model 18, fitting and prediction phase

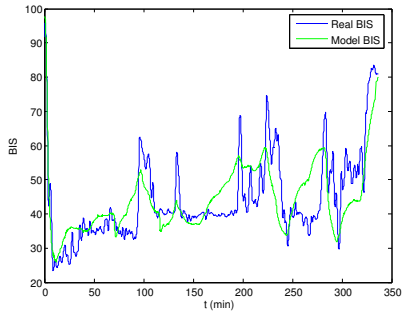


Fig. 7. Real (blue line) versus modeled (green line) BIS values for patient model 32, fitting and prediction phase

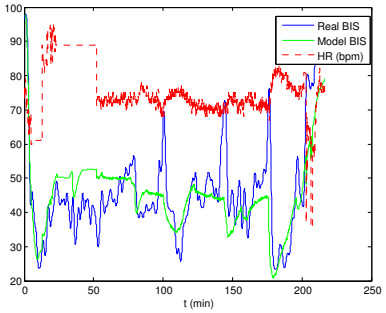


Fig. 8. Real (blue line) versus modeled (green line) BIS values, and heart rate (red line) for patient model 26, fitting and prediction phase

TABLE I

FUZZY C-MEANS ALGORITHM CLUSTER CENTERS FOR THE BIS MODEL PARAMETERS.

Cluster	EC_p	EC_{50r}	γ	$\beta_{2,U50}$
1	1.86	4.62	1.54	0.55
2	0.59	49.74	2.12	0.00
3	0.91	25.96	1.69	0.27

of propofol. This is in accordance with [6].
To identify if there were groups of patients, the fuzzy c-means algorithm was applied to the model parameters. The Xie-Beni [10] index was used to identify the adequate number of clusters. Three clusters were identified, table I shows the cluster centers.

V. CONCLUSIONS AND FUTURE WORKS

A. Conclusions

The induction phase of anesthesia can be used to establish the patient's individual response to the drugs. Dynamically adjusting the propofol potency (EC_{50p}) to the patient's heart rate improved the parameters identification. This model proved to be effective by adequately modeling the induction BIS trend in all 45 patients. Comparing with the work on [4], more models had statistical zero errors. In the prediction phase, 24 models had improved results, which were very significant in 8 of them. These results support the idea that heart rate has influence on the propofol dynamics, altering its absorption or distribution from the plasma to the brain (effect-site).
The fuzzy clustering algorithm showed the existence of 3 distinct clusters of models/patients, this information will help to distinguish between different patients' dynamics and help to build a bank of models more adequate for specific groups of patients improving the parameter identification procedure. The Marsh PK model for propofol [8] and the Minto PK model for remifentanil [9] are already credited and published models, available in commercial devices. However, the identification of the PK parameters could improved the results of the overall interaction model.

B. Future Works

The degree of resistance of the patient to the drugs has a great influence on the amount of drugs necessary during surgery to maintain an adequate level of unconsciousness and analgesia. Information extracted during induction can be used to adapt the infusion rates of both drugs, improving the patient's safety and comfort, avoiding cases of overdosage or awareness. The control system parameters can be adjusted or adapted to individual patient requirements. The existence of different groups of patients models may help to identify different control structures and improve the ability to adapt to specific patient responses.

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