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EMG contributes to improve Cerebral State Index modeling in dogs anesthesia

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Abstract—**Cerebral State Index (CSI) is a measure of depth of anesthesia (DoA) developed for humans, which is traditionally modeled with the Hill equation and the propofol effect-site concentration (*Ce*). The CSI has been studied in dogs and showed several limitations related to the interpretation of EEG data. Nevertheless, the CSI has a lot of potential for DoA monitoring in dogs, it just needs to be adjusted for this species. In this work, an adapted CSI model is presented for dogs considering a) both Ce and EMG as inputs and b) a fuzzy logic structure with parameters optimized using the ANFIS method. The new model is compared with traditional Hill model using data from dogs in routine surgery. The results showed no significant impact in the model performance with the change of model structure (Fuzzy instead of Hill). The residuals of the Hill model were significantly correlated with the EMG, indicating that the latter should be considered in the model. In fact, the EMG introduction in CSI model significantly decreased the modeling error: 11.8 [8.6; 15.2] (fuzzy logic) versus 20.9 [16.4; 29.0] (Hill). This work shows that CSI modeling in dogs can be improved using the current human anesthesia set-up, once the EMG signal is acquired simultaneously with the CSI index. However, it does not invalidate the search of new DoA indices more adjusted to use in dog's anesthesia.**

I. Introduction

Automatic systems to monitor depth of anesthesia (DoA) are essential in the operating room, diminishing anesthesia side effects [1]. DoA monitors provide a friendly display of an electroencephalogram (EEG) derived index, since increased DoA has been associated with decreased brain electrical activity [1]. The validation of a DoA index can be carried out, e.g. with models that estimate this index as a function of physiological variables rather than those derived from the EEG. Traditionally, DoA indexes are modeled with the Hill equation and consider propofol effect-site concentration (*Ce*) as input [2].

The Cerebral State Index (CSI) was developed to monitor human DoA, but is also used in veterinary anesthesia [3]. The increasing advances in human anesthesia were not totally followed by veterinary anesthesia and, therefore, there is a relevant gap concerning monitoring of cerebral depression in dogs anesthesia. Thus, it is imperative to improve animal's safety through the development of DoA indices adjusted to this species.

Although hypnotics are not muscle relaxants, they induce muscle relaxation at high doses that can be evaluated by the electromyography (EMG). DoA monitors acquire a signal of electrical activity from facial electrodes and make use of band pass filters to obtain EEG and EMG data [4]. Because EEG and EMG frequency bands are overlapped above approximately 30 Hz [5], it is possible that the EMG acquired by DoA monitors contains EEG information of high frequencies. Also, as indicated by Jensen et al [6]: "It cannot be ruled out that the CSI has some influence of facialis electromyography". These observations led us to study the hypothesis of enhancing CSI modeling by taking into account EMG data, besides *Ce*.

The CSI and *Ce* relation is sigmoidal-like, justifying the use of the Hill model. As EMG is introduced in CSI model as another input, a new model structure had to be considered. However, there is no established relationship between these three variables. In this framework, fuzzy logic methods were used to describe the unknown inputs-output relationship, combining both empirical rules (that were driven by the problem) and information extracted from the experimental data itself [7]. Another advantage of this method is related to the inter-variability between patients; this model weighs rules and permits a grey zone, not only "1" or "0", allowing better modeling of patients reaction. Fuzzy methods are easy to interpret as the model output can be written as a weighted linear combination of the system inputs.

In this work, a fuzzy logic model with inputs *Ce* and EMG is presented for dogs, and compared with the traditional Hill model. Additionally, to evaluate the methodology alteration impact in the model performance, a fuzzy logic model with input *Ce* is also considered.

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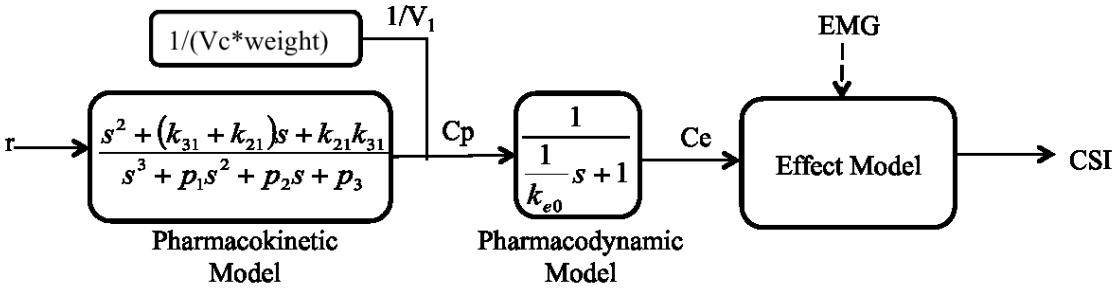

Fig. 1: Model scheme from the drug infusion rate (r) to the measured effect (CSI), the Cp corresponds to propofol plasma concentration, Ce corresponds to propofol effect-site concentration, k_{ij} represents the transfer rate from the compartment i to the compartment j, $p_1=k_{31}+k_{21}+k_{10}+k_{13}+k_{12}$, $p_2=k_{21}k_{31}+k_{10}k_{21}+k_{13}k_{21}+k_{10}k_{31}+k_{12}k_{31}$, $p_3=k_{10}k_{21}k_{31}$, V_c is the volume of central compartment per kg and *weight* is the dog's weight in kg. EMG is the electromyogram, which is not an input in the Hill model routinely used.

II. Methods

The process between the drug infusion rate r and the CSI are represented in Fig. 1. Briefly, after administration, the drug is distributed to and eliminated from the body, exerting its effect on the brain. The pharmacokinetic (Pk) model is described by Beths [8, 9], and allows the plasma concentration (Cp) estimation. The pharmacodynamic (Pd) model is presented by Brás [10], being used in the effect-site concentration (Ce) estimation. Finally, Ce is used as an input of the effect model that describes the CSI. Traditionally, this effect is described with the Hill equation (Sec. II A) and in this work a fuzzy logic approach is considered (Sec. II B).

A. CSI modeling with the Hill equation

The Hill model is described by

$$\hat{CSI}_t = CSI_0 + (CSI_0 - CSI_{max})\left(\frac{Ce_t^{\gamma}}{Ce_t^{\gamma} + EC_{50}^{\gamma}}\right) \quad (1)$$

where CSI_{max} is the CSI value at maximum drug effect, CSI_0 is the CSI at no drug, EC_{50} is the effect-site concentration that produces 50% of the maximum effect and γ is the Hill parameter that represents the steepness of drug effect at sigmoidal inflexion point. For each dog's data, the Hill equation parameters were identified using nonlinear least squares. The average parameters were used in a fixed parameter model.

B. CSI modeling with the fuzzy logic approach

Considering a Sugeno model with given inputs x_j ($j=1,2,...,n$), a typical rule i ($i=1,2,...,N$) has the form:

If $x_j \in F_i(x_j)$, then the output of the rule is

$$z_i = \sum_{j=1}^{n} a_j^i x_j + c_i \quad (2)$$

where $F_j^i(x_j)$ are fuzzy sets, a_j^i and c_i are constants [11]. The z_i of each rule is weighted by its firing strength w_i

$$w_i = \prod_{j=1}^{n} \Gamma_{F_j^i(x_j)} \quad (3)$$

where $\Gamma_{F_j^i}$ is a Gaussian membership function defined by its center μ_i and standard deviation σ_i [12]. The final output of the system $\hat{z}$ is the weighted average of all z_i, computed as

$$\hat{z} = \frac{\sum_{i=1}^{N} w_i z_i}{\sum_{i=1}^{N} w_i} \quad (4).$$

The parameters of the model (a, c, μ and σ for each rule i) were estimated using Adaptive Network Fuzzy Inference System (ANFIS), combined with backpropagation and least squares minimization (hybrid method) [11]. In this work, the initial μ and σ estimates were obtained from subtractive clustering. Briefly, the antecedent domain is divided in clusters. In this method, the radius σ is defined a priori as a value between 0 and 1, where 1 corresponds to the data range [13]. The initial radius σ was chosen from the set {0, 0.05, …, 1} as the radius that allowed to obtain the highest performance after ANFIS procedure.

The proposed fuzzy logic model with two inputs (model B) considers n=2 and x_1=EMG and x_2=Ce. For an adequate comparison with the traditional Hill model, in particular, to explore the differences between the models due to changes in methodology, a fuzzy logic model with single input Ce (model A) was additionally introduced, considering n=2 and x_1=EMG and x_2=Ce.

C. Performance evaluation

The performance of the models was evaluated in terms of the mean absolute error for each record, obtained from

$$error = \frac{1}{m}\sum_{t=1}^{m}\left|CSI_t - \hat{CSI}_t\right| \quad (5)$$

where m is the recording length, $\hat{CSI}$ is the estimate of CSI as provided by a model and t denotes time.

The errors were compared using nonparametric ANOVA for repeated measures, with significance level $p<0.05$ (Wilcoxon signed-rank for paired samples and Bonferroni correction for multiple comparisons).

III. Protocol & Clinical Data

Data were collected from 14 male dogs (*25.3±5.3 kg*), during routine surgery with general anesthesia using propofol 1% (Fresenius Kabi; Bad Homburg, Germany). The dogs were mixed breed, following the standard pre-intervention conditions [14].

During each intervention, propofol infusion rate $r(t)$,

CSI(t), and *EMG(t)* were simultaneously recorded on a 5 s time basis by the RugLoop II® software. Fig. 2 presents an illustrative example of a set of data acquired from one dog where it is possible to observe that an increase in *r(t)* produces an increase in *Ce(t)* and a decrease in both CSI(t) and EMG(t).

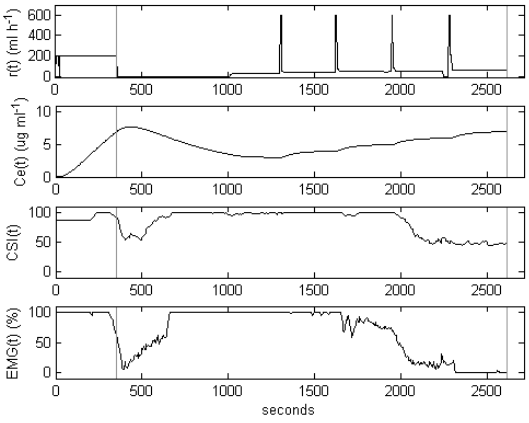

Fig. 2: Propofol infusion rate (*r*), *Ce*, CSI and EMG signals from Dog9. The first vertical lines correspond to the end of the induction phase and the second vertical line to the end of the maintenance phase. Variables *r*, CSI and EMG are recorded with the RugLoop II®, and the *Ce* is estimated using the methods in Sec. II.

The anesthesia was divided into Study and Surgical periods. The Study period was performed during induction and maintenance phases of anesthesia, where no external interferences occurred. In the induction phase, propofol was continuously administered at an infusion rate of *200 ml* h^{-1} until loss of clinical reflexes that allowed endotracheal intubation. In the maintenance phase, the propofol infusion rate was automatically adjusted to *Cp* targets stepwise increasing from *3* to *11* $\mu g\ ml^{-1}$. The propofol administration was interrupted if clinical signs of anesthetic depression occurred (hypotension or loss of corneal reflexes). After, the Surgical period began and the propofol was administered according to patient needs.

The original CSI sensors were adapted for animal use, as described in Bressan *et al* [15]. The wire link button was adapted to alligator's clamps, which were then clipped to the dog's head skin containing a conductor wax. The CSI and EMG were simultaneously acquired by the CSM monitor using the same sensors. The monitor collects an electrical signal from the head and makes use of digital filtering to obtain two signals: the EEG (6–42 Hz) and the EMG (75–85 Hz). The CSI index is then calculated from EEG frequency parameters and a multiparametric method based on fuzzy logic [4]. The numerical scale of CSI ranges from 0 to 100, where 0 indicates no brain electrical activity and 100 corresponds to awake state. The EMG is displayed as a numerical percentage (0–100 logarithmic), corresponding to the percentage of energy acquired in the 75–85 Hz frequency band divided by the total signal power [4].

IV. Results & Discussion

The fuzzy logic model with inputs *Ce* and EMG (model B) was compared with the traditional Hill model. Additionally, a fuzzy logic model with single input *Ce* (model A) was used. In all cases, the models parameters were identified in the Study period, ie, the phase with a standard administration protocol and no external interferences affecting the dog.

A different number of membership functions and rules were tested for model B, and the best performance was achieved with a 4 membership functions and 4 rules. Model B was given by

$$z_1 = 0.805\ EMG + 2.198\ Ce + 5.445\ ,$$
$$z_2 = 5.548\ EMG + 41.538\ Ce - 777.350\ ,$$
$$z_3 = 0.117\ EMG - 18.095\ Ce + 197.270\ ,$$
$$z_4 = -0.014\ EMG + 48.886\ Ce + 361.220\ ,$$

and weighted by:

$$\Gamma_{F^1_{EMG}} : \mu_1 = 83.001, \sigma_1 = 25.228, \Gamma_{F^1_{Ce}} : \mu_1 = 4.162, \sigma_1 = 4.303,$$
$$\Gamma_{F^2_{EMG}} : \mu_2 = 9.003, \sigma_2 = 25.234, \Gamma_{F^2_{Ce}} : \mu_2 = 5.945, \sigma_2 = 4.355,$$
$$\Gamma_{F^3_{EMG}} : \mu_3 = 34.060, \sigma_3 = 25.234, \Gamma_{F^3_{Ce}} : \mu_3 = 5.793, \sigma_3 = 4.460,$$
$$\Gamma_{F^4_{EMG}} : \mu_4 = 1.997, \sigma_4 = 25.218, \Gamma_{F^4_{Ce}} : \mu_4 = 3.644, \sigma_4 = 4.259.$$

Figure 3a) highlights the CSI association with both *Ce* and EMG and shows that the new model B follows adequately the experimental data. In accordance with physiology [6], the new model provides the highest modeled CSI values for the highest EMG and lowest *Ce* values. However, the extrapolation analysis of the new model may conduce to misleading interpretations in the EMG zero plane. As observed in Fig. 3a), the new model provides the lowest modeled CSI values for the lowest *Ce* values. However, the

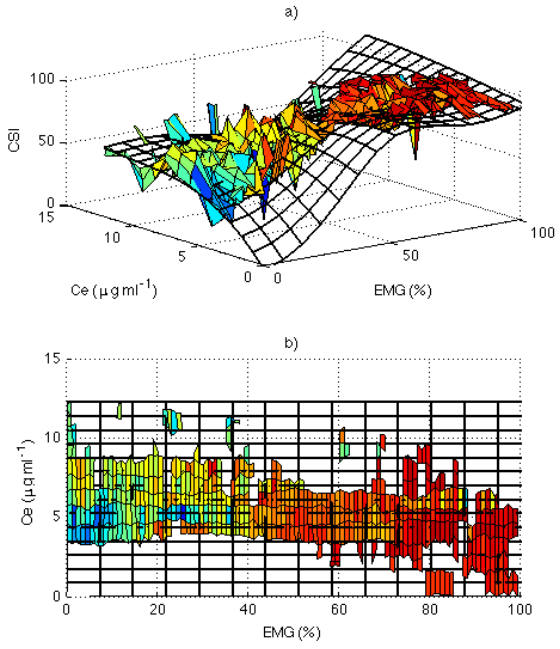

Fig. 3: Superimposing all dogs' CSI data and fuzzy logic model B represented as: a) a grid around the experimental data, and b) upside view showing, exhibiting the relation between *Ce* and EMG Study period.

lowest *Ce* values are associated with high EEG activity, once increasing concentrations of hypnotics induces EEG depression. In fact, it is possible to observe from Fig. 3b) a shift of the model estimates towards the highest EMG values and the lowest *Ce* values for the highest CSI values. This result indicates that in the presence of low *Ce* values, the EMG is the variable with more importance in the CSI modeling.

The model B was compared with the traditional Hill model. In the study period, the correlation between the Hill model residuals ($CSI - \widehat{CSI}$) and the EMG was found to be significant for all dogs, evidencing the importance of the EMG inclusion in the model (Fig. 3). Additionally it was compared with model A (the fuzzy model with single input *Ce*) to evaluate the impact of performance by changing the model structure, from Hill to fuzzy logic. As illustrated in Fig. 4, CSI estimates provided by both Hill and A models decrease with increasing *Ce*. Although model A does not assume a sigmoidal *Ce*/CSI relation as the Hill model does, the results evidenced a sigmoidal-like shape between *Ce* and CSI.

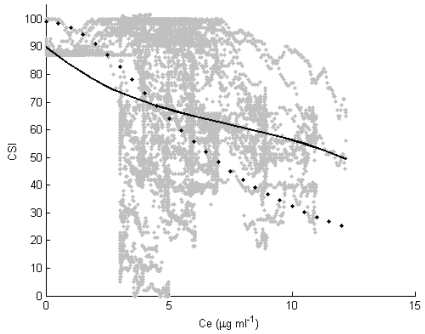

Fig. 4: Superimposing all dogs' CSI data in the Study period (in grey), Hill model (dotted black line) and model A (black line).

Figure 5 resumes the results from the statistical comparison of the models, distinguishing the Study and Surgical periods. There were found no significant differences between the performances of Hill and A model, therefore indicating no performance impact lead by changes in the model structure ($p>0.04$, Wilcoxon). Also in the Study period, the model B was found to exhibit a significant lower error when comparing to both Hill and A model ($p<0.008$), once more evidencing the importance of including the EMG in the CSI model. During the Surgical period, there were found no statistical differences between the three models indicating that the new model B has similar performance to that of the traditional Hill model. However, it was found that in 9 out of the 14 dogs, model B achieved lower modeling error than that of Hill model.

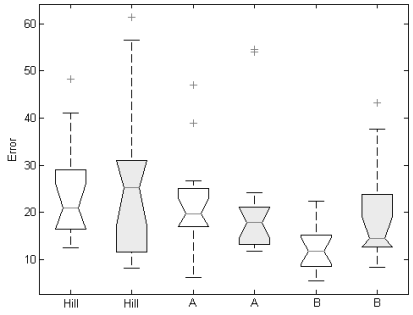

Fig. 5: Boxplot of the error (eq. 5) obtained from Hill, A and B models, for the 14 dogs. Error evaluated in Study (white) and Surgical (grey) period. Notches in the boxplot represent a robust 95% confidence interval for the medians for box-to-box comparison.

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