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# Data-based Pharmacodynamic Modeling for BIS and Mean Arterial Pressure Prediction during General Anesthesia\*

Bob Aubouin–Pairault<sup>1,2</sup>, Mirko Fiacchini<sup>1</sup>, Thao Dang<sup>2</sup>

**Abstract**—In this paper, a data-based approach is used to predict the effect of Propofol and Remifentanyl on Bispectral Index (BIS) and Mean Arterial Pressure (MAP) during total intravenous anesthesia. In particular, we aim to reproduce the measured data by identifying the pharmacodynamic function using machine-learning techniques. Features from the output of classic pharmacokinetic models and patient information are considered. Five learning methods are tested including linear models, support vector machine, Kernel,  $k$ -neighbors regressors, and neural-network. Learning and testing are performed on a particular subset of 150 surgery cases extracted from the VitalDB database. Results show that this approach improves the classic surface-response model for BIS and MAP prediction and can be used for anesthesia control applications.

**Keywords:** Anesthesia, Machine learning, Prediction, Pharmacodynamic, Hybrid model.

## I. INTRODUCTION

During general anesthesia, one of the anesthesiologist’s tasks is to continuously regulate intravenous drug rates to set hypnotic and analgesic levels to desired values while maintaining hemodynamic and respiratory variables stable. Since the development of fast-acting intravenous drugs like Propofol and Remifentanyl combined with reliable hypnotic indicators based on EEG signals like Bispectral Index (BIS), many models have been proposed to predict the influence of the drugs on the patient’s physiological state [1], [2].

The development of drug dosing models aims to improve patient recovery by aiding practitioners in optimizing drug administration. The standard practice of anesthesia currently involves Target-Control-Input (TCI) pumps [3], which allow the anesthesiologist to choose an effect-site drug concentration ( $C_e$ ) for each drug. The TCI then sets a drug rate to achieve the desired  $C_e$  according to a given model in an open-loop manner. Then the loop is closed by the anesthesiologist to obtain the desired levels of hypnosis and analgesia. While TCI has already improved the practice of anesthesia, some researchers are interested in closing the control loop to fully automate the drug dosage. Up to now, studies have shown the advantage of closed-loop control for anesthesia drugs [4], [5], but further research is needed to develop an optimal and reliable control method [6]. Other

researchers are also interested in detecting anomalies during surgery in order to preserve the vigilance of anesthetists on potential critical events [7].

One of the main sources of complexity in these research fields is the uncertainty affecting the models used to describe the influence of drugs on vital signals. In fact, the inter- and intra-patient variability of the physiological effects along with the exogenous disturbances coming from the surgeon’s actions makes difficult the task of predicting drug influences. As a consequence, standard models may not always be capable of accurately reproducing the measured data. Drug models are usually composed of two parts: Pharmacokinetic (PK) and Pharmacodynamic (PD). First, PK models describe the dynamics of drug concentrations in the patient’s body and are used by TCI devices. PD models describe the link between plasma drug concentrations and a given physiological effect. In the most used models, PK is described by a three-compartment system while PD is represented as a Hill-curve function that can take into account interactions between drugs. In practice, due to the lack of direct measurements of drug concentrations, it might be impossible to identify at the same time the parameters of both the dynamic model (PK) and the output function (PD).

In this paper, we propose to identify a PD output function, using machine-learning methods with measured data, which is able to model the overall effects of the uncertainties. Indeed, as PK models are already used and accepted by practitioners, we choose to work with the PK outputs and focus only on modeling the PD part. The resulting model is validated and can be used to predict BIS and Mean Arterial Pressure (MAP) during general anesthesia conducted with Propofol and Remifentanyl. More concretely, PK outputs and patient personal data are used as features for five different learning methods: ElasticNet linear regression,  $k$ -neighbors regression, support vector regression, kernel-based regression, and recurrent neural network. Note that such hybrid modeling, combining a linear system for the dynamics of the system and learning techniques to model the output, has already been studied by Gambus *et al.* [8] where an Adaptive Neuro Fuzzy Inference System is used to predict the BIS from effect-site concentrations. Nevertheless, this method does not consider patient personal data as input to obtain an individual model. Other data-learning techniques to predict BIS and MAP have also been studied in [9], [10], and [11], but the models obtained in these papers are complete black-boxes and are not suitable

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to be used for other applications, such as closed-loop control.

This paper is organized as follows. In Section 2 the standard PK-PD model is recalled, then in Section 3 the dataset creation, the learning methods, and the performance evaluation are detailed. Finally, Section 4 presents the obtained results and Section 5 provides some concluding remarks.

## II. STANDARD MODELS

### A. Pharmacokinetic Models

The most common PK model is a three-compartment model with compartments representing blood, muscle, and fat drug concentrations, each characterized by constant volume and clearance rate ( $V_i, Cl_i$ ). This results in a linear model described by equations:

$$\begin{pmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \\ \dot{x}_3(t) \end{pmatrix} = \begin{pmatrix} -(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} + \begin{pmatrix} \frac{1}{V_1} \\ 0 \\ 0 \end{pmatrix} u(t) \quad (1)$$

Where  $x_1(t)$ ,  $x_2(t)$  and  $x_3(t)$  respectively represent drug concentrations in blood, muscle, and fat, measured in  $[mg/l]$ . The coefficients, all measured in  $[l/min]$ , are given by:

$$\begin{aligned} k_{10} &= \frac{Cl_1}{V_1}, k_{12} = \frac{Cl_2}{V_1}, k_{13} = \frac{Cl_3}{V_1}, \\ k_{21} &= \frac{Cl_2}{V_2}, k_{31} = \frac{Cl_3}{V_3} \end{aligned} \quad (2)$$

The input  $u(t)$  is the drug infusion rate in  $[mg/min]$ .

Several studies have been conducted in order to link the patient personal data (age, height, weight, and sex) to the model parameters. If the most famous are the models developed by Schnider, Marsh, and Minto in [12] and [13] for Propofol and in [14] for Remifentanil, two more recent studies carried out by Eleveld and co-authors in [15] and [16] gather much more data and can be considered as the new state of the art on the subject. In this paper, three combinations of PK models are compared to test the performance of the different models.

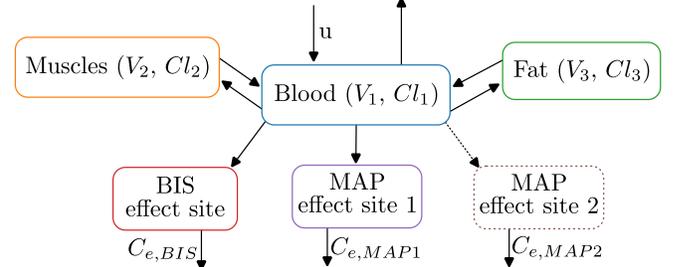
### B. Pharmacodynamic models

PK models link drug injection rates to blood concentrations. To describe the effect of the blood drug concentration on the BIS and MAP values, PD models are split into two parts. First, an effect-site compartment is used to express the delay between a variation in the blood concentration and the onset of the effect. This is expressed by equation (3).

$$\dot{x}_e(t) = k_e(x_1(t) - x_e(t)) \quad (3)$$

Due to the delayed effects of drugs on BIS and MAP (usually there is a 2-3 minute delay between Propofol blood concentration stabilization and BIS stabilization and

approximately 7 minutes for hemodynamics variables), at least two different effect sites for each drug must be used. For the influence of Propofol on MAP, Jelezcov *et al.* [17] proposes to use two distinct effect sites. These new compartments can be added to the PK models to obtain a five-compartment model for Remifentanil and a six-compartment model for Propofol (see Fig. 1).



**Fig. 1:** Scheme of the final compartments model, the second MAP effect site is used only for Propofol.

For BIS, the effect-site concentration is linked to the effect via a Hill function. Because there is a synergy between Propofol and Remifentanil the effect can be modeled as a response surface [18]:

$$BIS(t) = BIS_0 - E_{max} \frac{U(t)^\gamma}{1 + U(t)^\gamma} \quad (4)$$

where  $BIS_0$  is the initial BIS,  $E_{max}$  the maximum effect of combined drugs,  $\gamma$  the slope coefficient of the Hill curve and  $U(t)$  the interaction term defined by:

$$U(t) = \frac{U_p(t) + U_r(t)}{1 - \beta\theta(t) + \beta\theta(t)^2} \quad (5)$$

where:

$$U_p(t) = \frac{x_{ep}(t)}{C_{50p}}; U_r(t) = \frac{x_{er}(t)}{C_{50r}}; \theta(t) = \frac{U_p(t)}{U_p(t) + U_r(t)}$$

In these equations,  $x_{ep}$  and  $x_{er}$  are the Propofol and Remifentanil concentrations of the BIS effect site,  $C_{50p}$  and  $C_{50r}$  are the Propofol and Remifentanil half-effect concentrations for BIS (*i.e.* the concentrations to achieve half the effect of the drugs) and  $\beta$  is the interaction term between the two drugs. Parameters of [19] are used to compare all the models.

Concerning MAP, both Propofol and Remifentanil have a hypotensive effect, *i.e.* they lower the MAP values. However, there is no study on the interaction between Remifentanil and Propofol on this effect. Ionescu *et al.* [20] proposes to add the effect of the two drugs without interaction, using a sigmoid function to characterize the effect of each:

$$\begin{aligned} MAP(t) &= MAP_0 - E_{max,r} \frac{x_{er}(t)^{\gamma_r}}{C_{50r}^{\gamma_r} + x_{er}(t)^{\gamma_r}} \\ &\quad - E_{max,p} \frac{\frac{x_{e1p}(t)^{\gamma_{1p}}}{C_{50,1p}^{\gamma_{1p}}} + \frac{x_{e2p}(t)^{\gamma_{2p}}}{C_{50,2p}^{\gamma_{2p}}}}{1 + \frac{x_{e1p}(t)^{\gamma_{1p}}}{C_{50,1p}^{\gamma_{1p}}} + \frac{x_{e2p}(t)^{\gamma_{2p}}}{C_{50,2p}^{\gamma_{2p}}}} \end{aligned} \quad (6)$$

For Remifentanyl the parameters of the curves can be found in [21] and for Propofol in [17].

### III. METHOD

#### A. Dataset Creation

To create our dataset, the data from the *VitalDB* database [22] is used. This recent repository is the first open-source perioperative high-resolution database, it involves 6,388 surgical patients and is composed of intraoperative biosignals and clinical information. In order to get a dataset consistent with our objective, the first criterion to select cases is the inclusion of the desired features. For this, we select total intravenous anesthesia cases where MAP was invasively monitored through an arterial line to have a continuous measurement. However, we also include non-invasive MAP measures taken at the beginning of the procedure, to be used as MAP baseline. We additionally require that TCI data should be available, BIS and heart rate monitored during the procedure, and personal information available.

All the cases where Midazolam, Fentanyl, Epinephrine, Ephedrine, and Phenylephrine were injected in bolus are rejected due to the important impact of those drugs on BIS and MAP. Moreover, the cases where only Propofol and Remifentanyl were injected through TCI devices (no other drugs), and no inhalation drugs were administered, are selected to simplify the study. To keep the size of the dataset reasonable, 150 cases are selected through a visual inspection to reject the incoherent cases or the cases with a lack of data. Then the dataset is separated into 2 sets: 105 cases for training and 45 for testing. During this separation, a random seed is chosen to have approximately the same population demographic data in both sets, see Fig. 2.

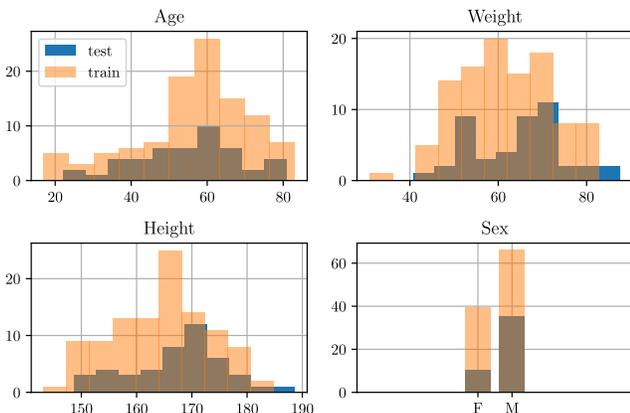


Fig. 2: Demographic data of the train and test datasets

To prepare the data, artifacts on the MAP signal are eliminated by suppressing points that exceed 50mmHg difference from the median value of the MAP for each patient. Additionally, BIS points with a signal quality index below 50 are removed. The BIS and MAP signals are then smoothed with a 20s exponentially weighted moving average and under-sampled by keeping only one point per minute.

#### B. Regression

Five different regression methods are used to predict BIS and MAP from different features, which will be detailed later on. These methods are Kernel Ridge Regression (KRR), ElasticNet, Support Vector Regression (SVR), K-neighbors regression (KNN), and Recurrent Neural Network (RNN). Among these methods, KRR, ElasticNet, and SVR are logistic regressors. In particular, ElasticNet is a linear model which proposes a mix between Ridge and Lasso regression, while KRR and SVR use the Kernel trick to represent non-linearity with a difference in the loss; KRR uses squared error loss and SVR uses epsilon-insensitive loss. KNN is a non-parametric model algorithm that predicts the target by local interpolation of the targets associated with the nearest neighbors in the training set. Finally, RNN is a deep-learning approach that can achieve higher performances at the cost of more training data and computing power. These regression methods have been chosen as part of the more commonly used, more details on these methods can be found in [23], [24] and [25].

The idea of using machine learning is to model the non-linear part of the existing model coming from the sigmoid function. The resulting model will have the same form as the standard one.

$$\begin{aligned} \dot{x}(t) &= A(\text{feat})x(t) + B(\text{feat})u(t) \\ y(t) &= f(x(t), \text{feat}) \end{aligned} \quad (7)$$

where  $\text{feat}$  is the vector of features that describe the patient: age, sex, weight, and height for standard models, and  $f$  is either the sigmoid function or our proposed machine learning function. The interest of having such a structure is that the whole dynamic part of the model is included in the linear model while the non-linear function only maps the state to the output and might be inverted using numerical methods. Thus, such a structure can be more efficiently used by other applications such as control with respect to more complex models, such as [9].

The following features are used for the regressions:

- $\text{age}, \text{sex}, \text{height}, \text{weight}, \text{BMI}, \text{LBM}$  to describe the patient's body.
- $\text{HR}$ : Heart Rate median value over the last ten minutes to characterize the hemodynamic system of the patient.
- $C_{\text{blood-propo}}, C_{e,\text{BIS-propo}}, C_{e,\text{MAP-propo}}, C_{\text{blood-remi}}, C_{e,\text{BIS-remi}}, C_{e,\text{MAP-remi}}$  are Propofol and Remifentanyl concentrations in blood, BIS effect site and MAP effect site, computed with Eleveled model, seemingly more precise.

This leads to a total of 13 features.

In the absence of a baseline MAP in the database, the first non-invasive MAP measure is selected as a substitute for standard model evaluation. In practice, a MAP baseline should be available as it is commonly measured

during the preoperative visit or just before anesthesia begins.

In the paper [9], Lee *et al.* give open-source access to their code, and this helps us reproduce their results and evaluate the performance of their deep-learning approach on our database. However, since the training of their neural network was not done with our training set, this evaluation is biased, in particular since Lee *et al.* used more training data and then there is the possibility that some of our test cases belong to their training set.

### C. Performance evaluation

To compare the performances of the different models, performance indices presented in [26] are used. First, the Performance Error (PE) in the percentage of each sample  $j$  is computed for each patient  $i$ :

$$PE_{i,j} = 100 \frac{y_{true,i,j} - y_{pred,i,j}}{y_{true,i,j}} \quad (8)$$

Median Predictive Error (MDPE) and Median Absolute Predictive Error (MDAPE) are computed for each patient as:

$$MDPE_i = median(PE_{i,*}), \quad MDAPE_i = median(|PE_{i,*}|)$$

Root Mean Squared Error (RMSE) is also computed for each case (not as a percentage value):

$$RMSE_i = \sqrt{\sum_{j=1}^{N_i} (y_{true,i,j}^2 - y_{pred,i,j}^2)} \quad (9)$$

Finally, the weighted mean and standard deviation of those metrics are computed to obtain the performances of the whole test population performance. Let us denote by  $M$  the number of cases and  $N_i$  the length of the  $i^{th}$  case, then:

$$MDPE = \frac{1}{\sum_{i=1}^M N_i} \sum_{i=1}^M N_i MDPE_i \quad (10)$$

$$SD(MDPE) = \sqrt{\frac{1}{\sum_{i=1}^M N_i} \sum_{i=1}^M \frac{N_i var_i(PE_{i,*})}{E_i}} \quad (11)$$

where  $var_i(PE_{i,j})$  is the variance of the performance error in the  $i^{th}$  patient and  $E_i$  is the statistical efficiency of the median of  $N_i = 2n_i + 1$  samples defined by:

$$E_i = \frac{4n_i}{\pi N_i} \quad (12)$$

Equivalent equations are used for the final MDAPE value. For RMSE, the following equations are used :

$$RMSE = \frac{1}{\sum_{i=1}^M N_i} \sum_{i=1}^M N_i RMSE_i \quad (13)$$

$$SD(RMSE) = \sqrt{\frac{1}{\sum_{i=1}^M N_i} \sum_{i=1}^M N_i (RMSE_i - RMSE)^2} \quad (14)$$

## IV. RESULTS

For the training of the five algorithms we use *scikit-learn* and *Pytorch* libraries on *Python* with grid search and cross validation to tune the main hyper-parameters. The code to generate the database, train the algorithms and obtain the final results is available on the GitHub repository, accessible from the following link: <https://github.com/BobAubouin/BIS-MAP-Pred/tree/0.1>. The final results are given in Table I.

First, considering the results of the standard models, one can observe that the pharmacokinetic models proposed by Eleveld *et al.*[16] [15] obtain the best score for BIS prediction. This was expected since this model has been fitted on a larger dataset than Schnider, Marsh, and Minto models [13], [12], [14]. However, the best score achieved by this model is an MDAPE of  $24.1 \pm 25.3$  for BIS prediction which seems a lot when the objective is usually to constraint the BIS in the interval between 40% and 60%. For MAP prediction, all the standard models obtain similar results which are worse than the BIS results. This can be explained by the fact that the effect of Remifentanyl and Propofol on MAP has been less studied than their effect on BIS, leading to less precise models. The second factor is that the MAP baseline taken as the first non-invasive measure might not be representative of the true MAP baseline.

Concerning the deep-learning model proposed by Lee *et al.* [9], results similar to those presented in their article are obtained (MDAPE of  $13.9 \pm 5.3$  for the maintenance phase in their paper, versus  $13.9 \pm 23.3$  in our evaluation). The large difference in standard deviation value could be explained by a different computation method or by the fact that our test dataset contains only 45 cases while there contains 100 cases.

Concerning our results, one can observe that all our regressors outperform standard models for BIS prediction and achieve performances almost as well as the deep-learning model. For MAP prediction, the MDAPE is divided by more than two, compared to standard models. Particularly, the best results are obtained with SVR both for BIS and MAP prediction. To compare the behavior of our best model, Fig. 3-6 plots BIS and MAP prediction results for the worst and best cases of SVR prediction. In these figures, one can notice that the MAP prediction does not fit well with the variation of measured MAP. This could be explained by the fact that external disturbances seem to affect the signal more than the effect of drugs. Thus, predicting MAP variation without knowing the stimulus affecting the patient might not be straightforward. Nevertheless, our model predicts a more precise average MAP value than standard models, which indicates an improved precision that could be useful.

One issue which appears sometimes with data-based models is the lack of consistency with true physiology.

Model	BIS			MAP		
	MDPE (%)	MDAPE (%)	RMSE	MDPE (%)	MDAPE (%)	RMSE
Marsh - Minto	$-29.7 \pm 36.5$	$32.9 \pm 31.7$	$15.8 \pm 5.9$	$21.2 \pm 16.2$	$26.7 \pm 12.8$	$26.1 \pm 11.5$
Schnider - Minto	$-28.4 \pm 38.6$	$31.8 \pm 32.5$	$16.2 \pm 5.4$	$21.7 \pm 15.2$	$26.4 \pm 12.4$	$25.9 \pm 11.3$
Eleved	$-13.3 \pm 28.4$	$21.4 \pm 23.3$	$11.3 \pm 3.8$	$24.4 \pm 14.2$	$28.3 \pm 11.5$	$27.4 \pm 11.8$
Lee <i>et al.</i> [9]	$-3.3 \pm 28.7$	<b><math>13.9 \pm 23.3</math></b>	$10.0 \pm 3.0$	-	-	-
ElasticNet	$-4.4 \pm 26.4$	$18.8 \pm 19.5$	$10.9 \pm 2.7$	$-0.5 \pm 15.6$	$10.9 \pm 10.7$	$12.9 \pm 3.3$
KNeighborsRegressor	$-2.3 \pm 28.3$	$14.9 \pm 20.8$	$10.0 \pm 2.3$	$0.3 \pm 15.5$	$10.7 \pm 10.5$	$12.9 \pm 3.5$
KernelRidge	<b><math>-0.7 \pm 29.7</math></b>	$15.2 \pm 23.9$	$10.0 \pm 3.8$	$0.3 \pm 16.1$	$10.9 \pm 11.2$	$13.3 \pm 3.5$
SVR	$-2.3 \pm 29.0$	$14.1 \pm 21.7$	$10.2 \pm 2.3$	$-0.5 \pm 14.1$	<b><math>10.0 \pm 10.0</math></b>	<b><math>11.8 \pm 3.4</math></b>
RNN	$-3.0 \pm 25.3$	$15.4 \pm 19.1$	<b><math>9.6 \pm 2.5</math></b>	<b><math>0.3 \pm 15.4</math></b>	$10.5 \pm 10.6$	$12.9 \pm 3.3$

TABLE I: Prediction performances of the different models on the test cases.

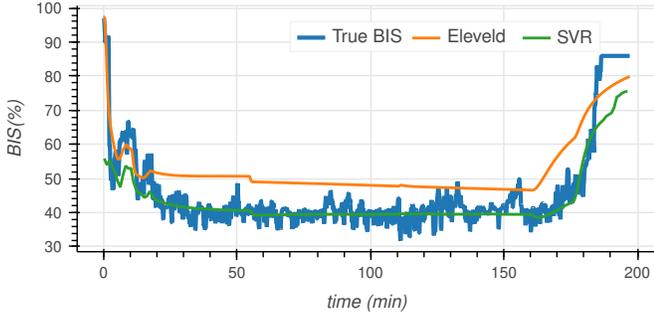


Fig. 3: Smoothed BIS measurement compared to BIS prediction for Eleved model and SVR, for the smallest RMSE of SVR

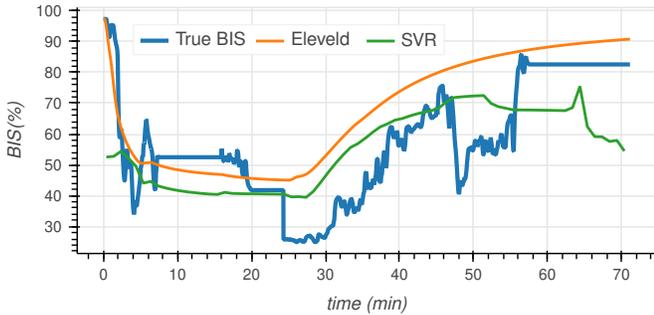


Fig. 4: Smoothed BIS measurement compared to BIS prediction for Eleved model and SVR, for the bigger RMSE of SVR

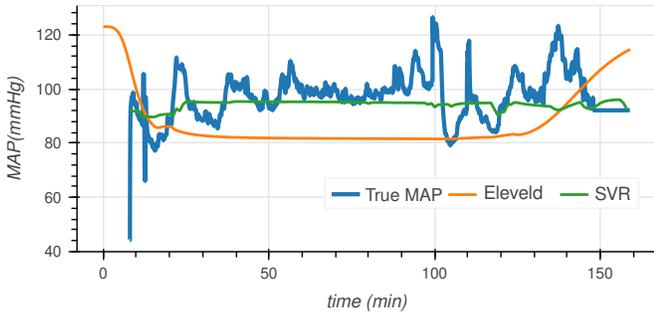


Fig. 5: Smoothed MAP measurement compared to MAP prediction for Eleved model and SVR, for the smallest RMSE of SVR

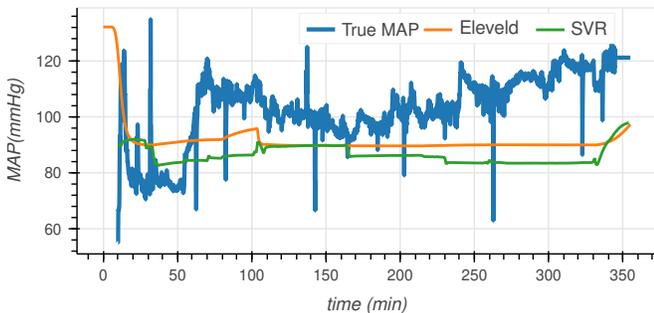


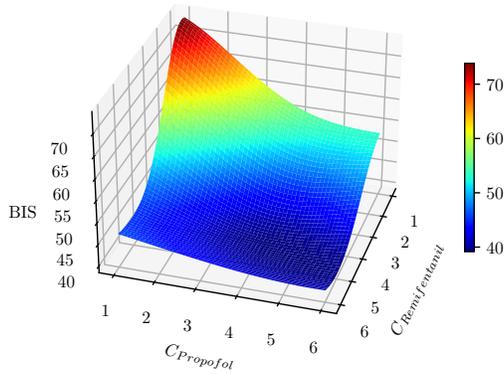
Fig. 6: Smoothed MAP measurement compared to MAP prediction for Eleved model and SVR, for the bigger RMSE of SVR

For instance, in terms of pharmacodynamics, several studies have concluded that both Propofol and Remifentanyl should reduce BIS and MAP values. However here due to exogenous disturbances affecting BIS and MAP during the surgery procedures, our model might learn something else. To verify this, the 3D response surface of the BIS is plotted with  $C_{blood-propo} = C_{e,BIS-propo} = C_{e,MAP-propo}$  and  $C_{blood-remi} = C_{e,BIS-remi} = C_{e,MAP-remi}$  for the SVR and RNN regressors on a reference individual (70kg male, 35 years of age, 170cm tall and a heart rate of 80bpm), see Fig 7-8. Here, one could observe that even if the RNN regressor has the smallest RMSE error for BIS prediction, its surface is not consistent with the prior knowledge. In fact, firstly Remifentanyl seems to have more effect than Propofol on BIS, and secondly, for a constant concentration of 6ng/mL of Remifentanyl, the curve indicates that Propofol seems to induce an increase in the BIS, which is not consistent with clinical knowledge. On the other hand, the surface generated by the SVR model seems quite close to the standard surface model even though Remifentanyl seems to have a bigger effect than in theory. Thus SVR appears to be a good candidate to be used for control-oriented applications.

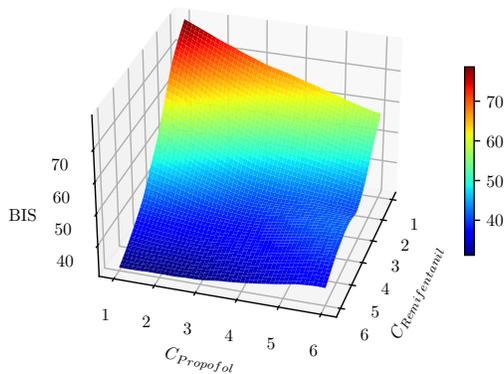
## V. CONCLUSION

In this paper, a new hybrid approach to predict Bispectral Index (BIS) and Mean Arterial blood Pressure (MAP) during general anesthesia has been developed. This approach uses the pharmacokinetics model outputs already employed in practice by anesthesiologists as inputs of the regressors to model the pharmacodynamics. Different regression techniques have been investigated and compared to standard surface response models and to a fully deep-learning approach. The obtained results show that all the proposed methods perform better than standard models, especially Support Vector Regression which seems to be the best option to predict both BIS and MAP with an accuracy almost as good as the evaluated deep-learning approach. Also, the use of heart rates past median value as a feature seems to provide useful information to the model and could be used in other model structures to reduce uncertainties.

The proposed hybrid model, which combines a well-established dynamical system with regressors as an output layer, will be used in future work to enhance closed-loop control methods and critical events detection algorithms.



**Fig. 7:** Static BIS surface response of a reference individual from SVR.



**Fig. 8:** Static BIS surface response of a reference individual from RNN regressor.

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