

# Comparison of Multi-EKF and MHE for PD parameter Estimation

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## 1 Introduction

This report details the pipeline for the comparison of the two methods to identify PD parameter from Propofol and Remifentanil using BIS as the measured signal. In order to have a fair comparison, this is done on simulated data, where the true parameters are known.

This report is organized as follow, Section 2 explain the method to generate the simulated data. Section 3 explain the details of the two proposed methods and the metrics used to evaluate the performances. The results are presented in section 4 and some conclusion are exposed in section 5.

## 2 Data generation

### 2.1 Drug model

In order to simulate the effect of Propofol and Remifentanil on the depth of hypnosis the standard pharmacokinetic-pharmacodynamic (PK-PD) structure is used. The PK part models the distribution of drugs in the body using a compartment-model resulting in two decoupled LTI system, one for each drug. The outputs of this models are two effect-site drug concentrations which can be linked to the hypnotic effect by the PD part using a surface model response to model the synergic effect between both drugs. The final, model can be expressed by the following equation:

$$\begin{aligned}\dot{x}(t) &= Ax(t) + Bu(t) \\ y(t) &= f(x(t)) + w(t)\end{aligned}\tag{1}$$

where  $x(t) \in \mathbb{R}^8$  represent the concentration of drugs inside the different compartments, particularly  $x_4(t)$  and  $x_8(t)$  are respectively the Propofol and Remifentanil effect-site concentration.  $u(t) = (u_p(t) \ u_r(t))^{\top}$  are the Propofol and Remifentanil drug rates injected into the patient blood.  $f$  is the surface model function that can be describe by the following equation:

$$f(x(t)) = BIS_0 + E_{max} \frac{I(t)^{\gamma}}{1 + I(t)^{\gamma}}\tag{2}$$

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:

$$I(t) = \frac{x_4(t)}{C_{50p}} + \frac{x_8(t)}{C_{50r}}; \quad (3)$$

$C_{50p}$  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).

Finally  $w(t)$  is the measurement noise. In the paper, a white noise filtered by a second order low pass filter with a cut-off frequency of 0.03 Hz is used to replicate real condition.

In the simulation, the parameters of [1] and [2] are used respectively for Propofol and Remifentanil PK model. For the PD model the parameters from [3] are implemented. To perform simulation as close to the reality as possible uncertainties are added to the parameters. Particularly, each parameter is following a log-normal distribution (parameters of the distribution are specified in the previously cited paper) and a realization of the distribution is used for each patient. Simulation are done using the Python Anesthesia Simulator [?].

## 2.2 Drug rates tunning

During the total intravenous anesthesia, Propofol and Remifentanil are dosed using Target Concentration Infusion (TCI) pumps. Those pumps include the nominal PK models, the anesthetist can select a concentration target and the pumps will compute and inject the drug to reach the target thanks to the model in an open loop matter. At the end the anesthetist is tuning the concentration target to reach the desired level of hypnosis.

In order to recreate this scheme of control, TCI control algorithm [4] have been reproduced. To reproduce the comportment of the anesthesiologist the following rules have been coded:

- At the beginning the target concentration are set to  $u_p = 4\mu\text{g}/\text{mL}$  and  $u_r = 4\text{ng}/\text{mL}$ .
- A control period is randomly draw for each patient and each drugs between 3 and 7 minutes. At each end of the period, the concentration target of the given drugs is updated as follow:
  - If  $55 < BIS$  the target is increased by 0.5.
  - If  $40 < BIS$  the target is decreased by 0.5.

In addition for Propofol only:

- If  $BIS > 60$  the target is increased by 1.
- If  $BIS < 40$  the target is decreased by 1.

An example of the resulting control is exposed Fig 1.

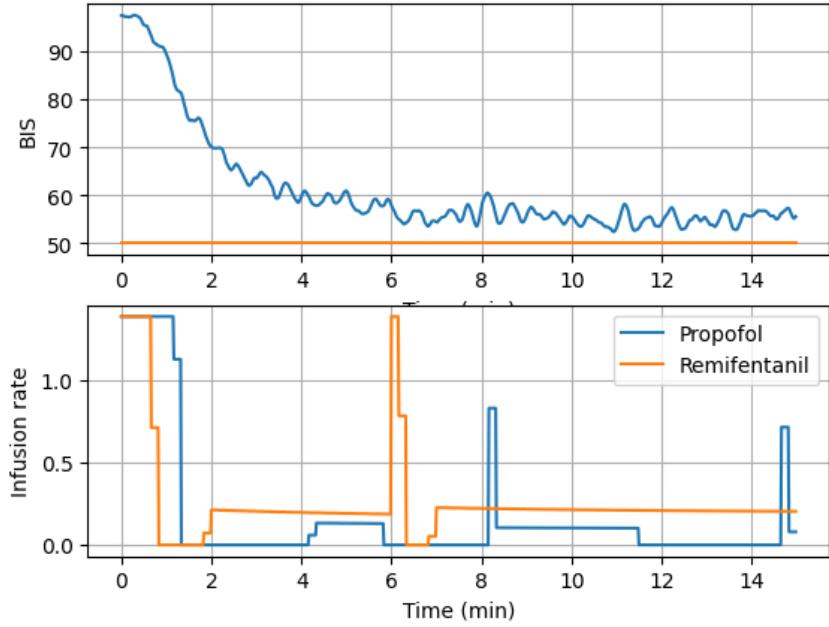


Figure 1: Results of the control algorithm for a single random patient.

### 2.3 Characteristics of the database

The final databased includes induction (15 minutes) simulation files for 1000 different patients with a sampling time of one second. Patients characteristic have been randomly chosen using uniform distribution ( $\text{age} \in [18, 70]$ ,  $\text{height} \in [150, 190]$ ,  $\text{weight} \in [50, 100]$ , and gender  $\in \{0, 1\}$ ). Each files includes all the signals from the simulator, particularly the BIS values and the drug rates over time are available. An additional file includes the parameters of each patient. Figures 2-4 expose the results of the simulations.

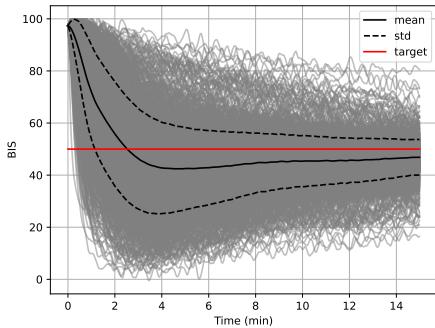


Figure 2: BIS trajectory for all the simu-

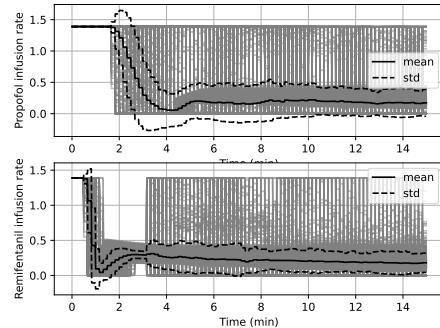


Figure 3: Drug input rates for all the simulations.

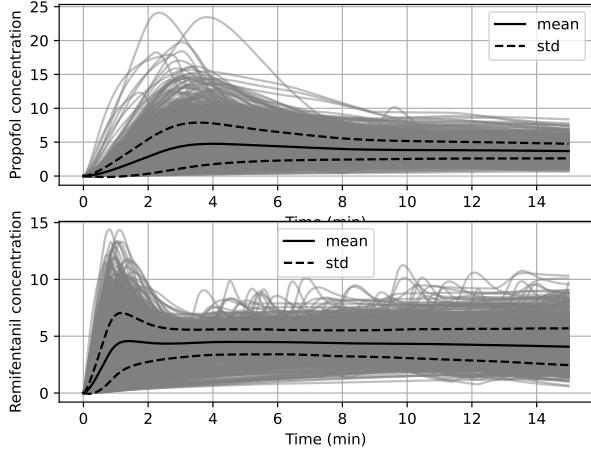


Figure 4: Drug effect-site concentration for all the simulations.

### 3 Methods

In this section, different methods used to estimate the unknown parameters of the PD models are detailed.  $BIS_0$  can be measured at before the induction of anesthesia and  $E_{max}$  is usually set equal to  $BIS_0$ . Thus the remaining parameters are  $C_{50p}$ ,  $C_{50r}$ , and  $\gamma$ . in this section,  $\theta = (C_{50p} \ C_{50r} \ \gamma)$  is used to describe the vector of unknown parameters.

The Multi Extended Kalman Filter (MEKF) method select the best vector among a grid in space of the parameters. This discrete choice allow a fast convergence but less precision at the end. The Moving Horizon Estimation (MHE) method uses an extended state formulation to estimate the vector of parameters along with the state in a continuous manner. Thus the method could identify more precisely the parameters but is also more subject to noise and could be slower than MEKF.

#### 3.1 Multi Extended Kalman Filter

In order to identify the PD parameters, the MEKF method uses a set of EKF, one for every realization of the vector selected within a grid in the space of the parameters. The grid is designed to reasonably represent the variability of the parameter vector. Next, a vector is chosen using a model-matching criterion.

EKF is a state estimation method that relies on the linearization of a non-linear model. If we consider the model given in (1) with the non-linear function  $f$  parametrized by  $\theta$ , the estimator using the parameter vector  $\theta_i$  is given by:

$$\begin{aligned}
H_i(k) &= \left. \frac{\partial f(x, \theta_i)}{\partial x} \right|_{x=\hat{x}_i(k_{|k-1})} \\
K_i(k) &= P_i(k_{|k-1}) H_i^\top(k) (H_i(k) P_i(k_{|k-1}) H_i^\top(k) + R_2)^{-1} \\
\hat{x}_i(k_{|k}) &= \hat{x}_i(k_{|k-1}) + K_i(k) (y(k) - f(\hat{x}_i(k_{|k-1}), \theta_i)) \\
P_i(k_{|k}) &= P_i(k_{|k-1}) - K_i(k) H_i(k) P_i(k_{|k-1}) \\
\hat{x}_i(k+1_{|k}) &= A \hat{x}_i(k_{|k}) + B u(k) \\
P_i(k+1_{|k}) &= A P_i(k_{|k}) A^\top + R_1
\end{aligned}$$

Here the notation  $X(k_{1|k_2})$  represents the value of variable X computed at time step  $k_1$  based on the knowledge available at  $k_2$ . The estimated state vector is  $\hat{x}$  and  $P$  is the covariance matrix.  $R_1$  and  $R_2$  are two constant matrices used to respectively characterize the process uncertainties and the measurements noise.

The idea is to select the "best" observer at each step time. To do so the estimation error on the output  $e_k = y_k - f(x_{k|k-1}, \theta_i)$  is used to construct a selection criterion. As in [5]

### 3.2 Moving Horizon Estimation

The Moving Horizon Estimator (MHE) is a dynamic system state estimation method that operates by solving an optimization problem over a moving time horizon. The optimization problem here lies in minimizing a cost function representing the discrepancy between the predicted model states and the actual measurements. The estimated states are recursively refined and updated using a combination of measured data and a mathematical model of the system. This consequently provides an accurate real-time assessment of the patient's physiological condition.

In the context of this paper, the MHE is used to estimate the states and the pharmacodynamics (PD) of an anesthesia model based on simulated data with known parameters. Being a model-based estimation approach, the MHE utilizes a linear PK-PD decoupled model linking the propofol and remifentanil infusion rates ( $u_p$  and  $u_r$ ) to their equivalent concentration in the effect site ( $x_{p4}$  and  $x_{r4}$ ) respectively:

$$\begin{pmatrix} \dot{x}_p \\ \dot{x}_r \end{pmatrix} = \begin{pmatrix} A_p & 0^{4 \times 4} \\ 0^{4 \times 4} & A_r \end{pmatrix} \begin{pmatrix} x_p \\ x_r \end{pmatrix} + \begin{pmatrix} B_p & 0^{4 \times 1} \\ 0^{4 \times 1} & B_r \end{pmatrix} \begin{pmatrix} u_p \\ u_r \end{pmatrix}$$

The model can hence be simplified as follows:

$$\dot{x} = A_T x + B_T U$$

With  $A_T \in R^{8 \times 8}$  and  $B_T \in R^{8 \times 8}$  represent the state and the input matrices.

The propofol PK-PD linear model is given as:

$$\begin{pmatrix} \dot{x}_{p1} \\ \dot{x}_{p2} \\ \dot{x}_{p3} \\ \dot{x}_{p4} \end{pmatrix} = \begin{pmatrix} -a_{11p} & a_{12p} & a_{13p} & 0 \\ a_{21p} & -a_{21p} & 0 & 0 \\ a_{31p} & 0 & -a_{31p} & 0 \\ a_{41p} & 0 & 0 & -a_{41p} \end{pmatrix} \begin{pmatrix} x_{p1} \\ x_{p2} \\ x_{p3} \\ x_{p4} \end{pmatrix} + \begin{pmatrix} \frac{1}{V_{1p}} \\ 0 \\ 0 \\ 0 \end{pmatrix} u_p$$

Similarly, the model can be simplified as follows:

$$\dot{x}_p = A_p x_p + B_p U_p$$

With  $A_p \in R^{4 \times 4}$  and  $B_p \in R^{4 \times 1}$  represent the state and the input matrices for propofol.

The linear PK-PD model for remifentanil follows a similar pattern.

The MHE offers robust state estimations in non-linear, uncertain, and constrained systems. In our case, the measured EEG signal is very noisy, so the MHE is expected to offer some benefits over the EKF that's considered to be aggressive as it allows to fit the output with the noise.

### 3.3 Metrics for the comparison

## 4 Results

## 5 conclusion

## References

- [1] D. J. Eleveld, P. Colin, A. R. Absalom, and M. M. R. F. Struys, “Pharmacokinetic–pharmacodynamic model for propofol for broad application in anaesthesia and sedation,” *British Journal of Anaesthesia*, vol. 120, pp. 942–959, May 2018.
- [2] D. J. Eleveld, J. H. Proost, H. Vereecke, A. R. Absalom, E. Olofsen, J. Vuyk, and M. M. R. F. Struys, “An Allometric Model of Remifentanil Pharmacokinetics and Pharmacodynamics,” *Anesthesiology*, vol. 126, pp. 1005–1018, June 2017.
- [3] T. W. Bouillon, J. Bruhn, L. Radulescu, C. Andresen, T. J. Shafer, C. Cohane, and S. L. Shafer, “Pharmacodynamic Interaction between Propofol and Remifentanil Regarding Hypnosis, Tolerance of Laryngoscopy, Bispectral Index, and Electroencephalographic Approximate Entropy,” *Anesthesiology*, vol. 100, pp. 1353–1372, June 2004.
- [4] S. L. Shafer and K. M. Gregg, “Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump,” *Journal of Pharmacokinetics and Biopharmaceutics*, vol. 20, pp. 147–169, Apr. 1992.
- [5] E. Petri, R. Postoyan, D. Astolfi, D. Nešić, and V. Andrieu, “Towards improving the estimation performance of a given nonlinear observer: A multi-observer approach,” in *2022 IEEE 61st Conference on Decision and Control (CDC)*, pp. 583–590, Dec. 2022.