Offset-Free Hybrid Model Predictive Control of Bispectral Index in Anesthesia

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Abstract— This paper deals with the anesthesia control, using bispectral index (BIS) as a measure of the depth of anesthesia; controlled by hybrid model predictive control strategy. The piecewise affine (PWA) hybrid pharmacodynamic model of a patient containing a set of local linear dynamics is used to describe the relationship between BIS value and drug infusion rate. The hybrid model predictive control problem is formulated as a mixed integer quadratic programming (MIQP) problem and solved online. Furthermore, a disturbance observer is designed for the offset-free BIS reference tracking, The results of designed controller intended for reference tracking, disturbance rejection and constraint handling are presented. Moreover, the performance of nonlinear MPC is compared with the hybrid MPC and is shown to be computationally less complex and fast.

I. INTRODUCTION

The barriers between control engineering and medicine are slowly eroding as it becomes more evident that control system technology has a great deal to offer medicine. Over the last decades, closed-loop control of anesthesia has received a considerable attention from researchers. Conventionally, the anesthesiologists used to decide the initial drug dose (bolus) by considering the patient's physical characteristics, such as gender, age, weight and height. During the period of surgery, anesthesiologists use to maintain anesthetic state based on patient's physiologic status such as blood pressure, heart rate, and breathing. Open-loop drug delivery control can lead to under- and over-dosing which can affect patient safety and increase anesthesiologists workload.

An automatic control system which can regulate drug delivery rate based on the anesthetic level can potentially improve the quality of surgical operations, patients safety, cost-effectiveness and reduce clinician's workload. It may reduce the risk of awareness and adverse outcomes during anesthesia, as well as reduce the health-care cost due to drugs, devices and recovery time. However, the realization of a safe and reliable closed-loop control of anesthesia is yet to be achieved due to a manifold of challenges. The main challenges in designing an automated closed-loop anesthesia delivery systems are i) to deal with non-linear, multi variable and interand intra-variability pharmacokinetic-pharmacodynamic (PK-PD) patient model; ii) selection of a controlled variable and its sensors that measure the relevant drug effect; iii) setting of clinically relevant set-point for this variable, which is the chosen target value specified by the anesthesiologist; iv) reliable actuator (the infusion pump driving drug administration); and v) design and implementation of a controller to manage the actuator, which comprises an algorithm for translating the measured value of the controlled variable to a particular action in order for the actuator to steer the controlled variable closer to the target value [1], [2].

The PK-PD model is the commonly used patient model in medicine to describe the dose-effect relationship of drugs in the human body. PK model is used to model and/or predict the disposition of the drug in the body, by modeling the simultaneous diffusion of drug through body tissues and the flow of drug in the blood. PD models are used to describe the relationship between drug concentration and the observed clinical effect; effect signals may be any number of patient vital signs and electroencephalogram (EEG) derived signals. These models are typically given by static nonlinear functions, which are used to describe the equilibrium relationship between the drug concentration, and drug effect. A commonly used pharmacodynamic model structure is given by the well-known Hill curve [3].

In general, the drug effect or the depth of anesthesia (DoA) is predicted, based on the feedback obtained from the linear PK model i.e. effect-site concentration and nonlinear PD model is just use to co-relate the effect-site concentration with the drug effect and it is not considered in a feedback loop. As a consequence of this structure (a linear block in series with a static nonlinearity), the prediction of human response to drugs cannot be accurately performed by linear model [4]. Based on this modeling approach, several classical and advanced control strategies has been designed and implemented in simulations. The earliest classical controllers designed for this system are fixed gain controllers like proportional-integral (PI) and proportional-integral-derivative (PID) [5]. Due to the fact that these controllers tend to poor performance in a case of robustness, stability, constraint handling and time delay systems, the advance controller like linear model predictive controller (MPC) which performs well for linear PK model and constraints satisfaction has been investigated in [6]-[9].

The attempts has been made to use approximated nonlinear PD model in the closed-loop control of anesthesia [10], [11]. In these research studies, linear MPC strategy was used to control the drug effect parameter. The presence of nonlinearities and constraints on one hand, and the simplicity needed for realtime implementation on the other, have discouraged the design of linear MPC for this kind of problem. Another way of dealing with this problem is by obtaining piecewise affine (PWA) hybrid model containing a set of local linear dynamics and the control of such systems lead to the hybrid model predictive control strategy [13], [14]. Recently, in [15] authors have demonstrated the applicability of explicit hybrid MPC for the control of anesthesia using PK-PD model presented in [11].

In this paper, we present a offset-free hybrid model pre-

dictive control (hMPC) strategy for the control of PWA hybrid anesthesia system. We used bispectral index (BIS) as a measure of DoA and Propofol as an anesthetic agent. Anesthesia control problem is formulated as a mixed integer quadratic programming (MIQP) problem and solved using online optimization method. We show the simulation results of designed controller intended for reference tracking, constraints handling, and disturbance rejection. The computational complexity of offsetfree hybrid MPC is compared with nonlinear MPC to show the capability of hybrid MPC for the real-time implementation on embedded hardware.

II. COMPARTMENTAL PK-PD PATIENT MODEL

This section comprised of two subsections. In the first subsection, we introduce a four compartment, single-input (drug infusion rate) single-output (effect-site concentration) PK model of the patient with Hill's sigmoid PD model to corelate output of PK model to clinical effect i.e. BIS index. Subsequently, in the second subsection, we describe the PWA hybrid model of the nonlinear PD model.

A. Nonlinear PK-PD Model

As for the pharmacokinetic model, we use four compartment model including the Propofol effect-site compartment based on the large-scale multi-center study by [16] which is further extended in [17]. The model seems to be sufficiently reliable, as its parameters were determined based on patient's real-time data and this model incorporates the patient's age and body weight (BW), so it can take individual differences into account to a certain extent. Fig. 1 shows the three compartment model with the effect-site compartment. It consists of central, shallow peripheral (fast), deep peripheral (slow) and virtual compartment regarded as effect-site. Peripheral compartment comprise muscle, fat, and other organs and tissues of the body which is metabolically inert as far as the drug is concerned. Shallow peripheral compartment represents tissues with a rich blood supply and deep peripheral compartment represents tissues with very poor blood supply.



Fig. 1. A block diagram of four-compartment PK-PD patient model showing drug concentration, volume, clearance and elimination.

The state space representation of the continuous-time pharmacokinetic model with the effect-site compartment is given by

$$\dot{x}(t) = Ax(t) + Bu(t), \tag{1a}$$

$$y(t) = Cx(t), \tag{1b}$$

where $x(t) \in \mathbb{R}^n$ is the system state vector of Propofol concentration in different compartments, $u(t) \in \mathbb{R}^l$ is the system input vector of Propofol infusion rate and $y(t) \in \mathbb{R}^m$ is the system output i.e. effect-site concentration, moreover, $A \in \mathbb{R}^{n \times n}$, $B \in \mathbb{R}^{n \times l}$ and $C \in \mathbb{R}^{m \times n}$ are system matrices as given below with the assumption that pair (A, B) is stabilizable and (C, A) is detectable

$$A = \begin{bmatrix} -\frac{k_1 + k_2 + k_3 + k_4}{V_1} & \frac{k_2}{V_1} & \frac{k_3}{V_1} & \frac{k_4}{V_1} \\ \frac{k_2}{V_2} & -\frac{k_2}{V_2} & 0 & 0 \\ \frac{k_3}{V_3} & 0 & -\frac{k_3}{V_3} & 0 \\ \frac{k_4}{V_4} & 0 & 0 & -\frac{k_4}{V_4} \end{bmatrix},$$
$$B = \begin{bmatrix} \frac{1}{V_1} & 0 & 0 & 0 \end{bmatrix}^T, \ C = \begin{bmatrix} 0 & 0 & 0 & 1 \end{bmatrix}.$$

here the subscripts 1, 2, 3, and 4 correspond to the central, shallow peripheral, deep peripheral and effect-site compartment, respectively. The parameter k and V are the clearance and volume of a different compartment, respectively, given as functions of patient's age and body weight. The relation between clearance, volume, age and weight can be found in [17][Table I]. The pharmacodynamic model represents relation between the effect-site concentration of Propofol and the BIS index value given by the following Hill's sigmoid $E_{\rm max}$ model

$$BIS(t) = E_0 - E_{\max} \frac{y(t)^{\gamma}}{y(t)^{\gamma} + c_{50}^{\gamma}},$$
(2)

where E_0 is the BIS value before starting the Propofol infusion, E_{max} is the change of the BIS index corresponding to the infinite Propofol concentration, C_{50} is the effect-site concentration corresponding to $\frac{E_{\text{max}}}{2}$, and γ is the Hill's coefficient. In this paper, we assume $E_{\text{max}} = E_0$. The control objective is to manipulate the Propofol infusion rate such that the BIS index tracks a prescribed reference. In the above model, we assumed baseline value equal to maximal output value and default values of C_{50} and γ are taken from [17].

BIS is an EEG-derived index which indicates the effect of drug on the body and measured on the scale of 0 - 100. BIS values near 100 represent an "awake" clinical state while 0 denotes the maximal EEG effect possible (i.e., an isoelectric EEG) which means the patient is in the dead state. In general surgery practice, the BIS value is maintained in the range of 40 - 60 to ensures adequate hypnotic effect during balanced general anesthesia while improving the recovery process. The drug dose below 60 is regarded as under dose where patient can respond to surgical stimuli and can feel pain. BIS index values lower than 40 signify a greater effect of the drug on the EEG of a patient and drug dose is regarded as overdose.

In general, targeted BIS value can be achieved by tracking corresponding effect-site compartment concentration and substitute that value in the (2) to get BIS value. It has been seen that this approach leads to inaccurate measurement of BIS values due to skipping nonlinear PD model from the feedback loop. One might consider PD model in the feedback loop which will turn into the nonlinear optimization problem. To solve this issue we will use piecewise linear (affine) models linearized from nonlinear PD model. In the next, we will describe PWA modeling of a anesthesia system.

B. Piecewise Linear PK-PD Model

As mention in the previous section, the relationship between drug concentration (effect-site compartment) and clinical effect (BIS) is mathematically given by nonlinear expression (2) and graphically as shown in Fig. 2 The nonlinear relationship between the effect-site compartment concentration and BIS is linearized by using the piecewise affine transformation of nonlinear response. In this task, the nonlinear Hill's curve was first divided into three pieces and then each piece was linearized by data fitting technique to find the coefficients of a polynomial function (BIS(t)) of degree 1 that fits the Hill's curve data best in a least-squares sense. The procedure was repeated by dividing curve into five pieces to get another PWA model. Here, we used MATLAB's "polyfit" function to find the coefficients of the PWA functions from Hill curve data. Fig. 2 shows the PWA models obtained after data fitting for three and five regions of original Hill's curve. It can be observed that the PWA model with five coefficients fits better to the original nonlinear curve but at the same time increases the complexity as compared to the three coefficient model which fits almost same in the upper part of the curve. So, in the controller design, we focused on PWA model with three regions. The piecewise linearized version of the Hill's curve



Fig. 2. PWA models of nonlinear Hill's curve. PWA models when Hill curve (blue) is divided into three (magenta) and five (red) regions.

is given as follows:

$$BIS(t) = a_i y(t) + b_i \quad \text{if} \quad y(t) \in \mathcal{P}^i, \tag{3}$$

where $\{\mathcal{P}^i\}_{i=1}^n$ is the *i*th polyhedral partition in the output space (effect-site concentration) defined as the intersection of finite number of half-spaces, which can be compactly defined as follows

$$\mathcal{P} = \{ y \in \mathbb{R}^m : Hy \le h \}, \tag{4}$$

where matrices $H \in \mathbb{R}^{r \times m}$, $h \in \mathbb{R}^{r \times m}$ are representing collection of intersecting affine half-spaces.

III. OBSERVER DESIGN

One of the key challenges for the design of drug delivery systems for anesthesia is high inter- and intra-patient variability, which introduces a high degree of uncertainty into the system. Therefore, the control design should be robust against implying uncertainty and tested for the uncertain system. In brief, we want a controller which guarantees constraint satisfaction for all admissible values of uncertainty and optimally steers the system to the desired BIS value. The uncertainty can originate from the model-mismatch (change in input parameters of model, i.e. age and weight), non-captured hidden process dynamics and input or output disturbances. To achieve offset-free controller, discretized version of the plant model (1) is augmented with a disturbance vector $d(t) \in \mathbb{R}^p$ [18, Chapter 13] as shown below

$$x(t+T_s) = Ax(t) + Bu(t), \tag{5a}$$

$$d(t+T_s) = d(t),\tag{5b}$$

$$y(t) = Cx(t) + C_d d(t), \tag{5c}$$

where $C_d \in \mathbb{R}^{m \times p} = I$ is the disturbance model output matrices and T_s is the sampling time. For the simplicity augmented model can be represented as follows

$$\begin{bmatrix}
x(t+T_s) \\
d(t+T_s)
\end{bmatrix} = \begin{bmatrix}
A & 0 \\
0 & I
\end{bmatrix} \begin{bmatrix}
x(t) \\
d(t)
\end{bmatrix} + \begin{bmatrix}
B \\
0
\end{bmatrix} u(t), \quad (6a)$$

$$u_c(t) = \begin{bmatrix}
C & C_d
\end{bmatrix} \begin{bmatrix}
x(t) \\
x_e(t)
\end{bmatrix} \quad (6b)$$

$$\underbrace{\bigcup_{C_e} a_t}_{x_e(t)} \underbrace{\bigcup_{x_e(t)} a_t}_{x_e(t)}$$

where 0 and I are the null and unit matrices/vectors of appropriate size. The subscript 'e' denotes the extended version of the combined state and disturbance.

The objective of estimator is to estimate the current states of the system and remove any control offset which may arise during the reference tracking. Extended state x_e is estimated from the plant measurement by designing a Luenberger observer for an augmented system (6) as follows

$$\hat{x}_e(t+T_s) = A_e \hat{x}_e(t) + B_e u(t) + L_e(y(t) - \hat{y}_e(t)),$$
(7a)
$$\hat{y}_e(t) = C_e \hat{x}_e(t),$$
(7b)

where $L_e = \begin{bmatrix} L_x & L_d \end{bmatrix}^T$ is the filter gain matrices for the state (of dimension $n \times m$) and the disturbance (of dimension $p \times m$), respectively and can be obtain by pole placement or quadratic estimation methods. Please note that the y(t) is not a measured signal in this setup and therefore it needs to be computed from (2) based on measurement of BIS(t).

IV. HYBRID MODEL PREDICTIVE CONTROL

The intravenous anesthesia control of a BIS based on the mathematical model of the patient as given in the Section II-A can be cast as a following nonlinear optimal control problem

$$\min_{u_0,\dots,u_{N-1}} \sum_{k=0}^{N-1} \left(||BIS_k - BIS_{\text{ref}}||_Q^2 + ||\Delta u_k||_R^2 \right)$$
(8a)

s.t.
$$x_{k+1} = Ax_k + Bu_k$$
, (8b)
 $d_{k+1} = d_k$, (8c)

$$u_{k+1} = u_k, \tag{8c}$$

$$y_k = Cx_k + C_d d_k, \tag{8d}$$

$$BIS_k = E_0 - E_{\max} \frac{y_k^{\gamma}}{w_k^{\gamma} + e^{\gamma}}, \qquad (8e)$$

$$y_{k'} + c_{50}$$

$$\Delta u_{k} = u_{k} - u_{k-1}$$
(8f)

$$\underline{u} \le u_k \le \overline{u},\tag{8g}$$

$$\Delta u < \Delta u_k < \overline{\Delta u}, \tag{8h}$$

$$x_0 = \hat{x}_e(t), \tag{8i}$$

$$u_{-1} = u(t - T_s), \tag{8j}$$

where x_k , u_k , y_k , and BIS_k represent the values of states, inputs, outputs and the bispectral index, respectively, predicted at the k^{th} step of the prediction horizon N and all constraints in (8b)–(8h) are enforced for k = 0, ..., N-1. The predictions are obtained from the LTI prediction model given by the equations (8b), (8d) and from nonlinear equation (8e). The difference of the control actions is given by (8f). The min/max constraints for the control input amplitude and difference are given by (8g) and (8h), respectively. The initial conditions of the problem (8i) are given as the state estimates from the estimator. For a particular initial conditions, the optimization procedure computes the sequence u_0^*, \ldots, u_{N-1}^* of control inputs that are optimal with respect to the quadratic objective function (8a) and the constraints. The term $||a||_Q^2$ in the objective function represents the weighted squared 2-norm, i.e., $a^T Q a$, with the positive definite diagonal weighting matrix Q. The first term of the quadratic cost function minimizes the square of the differences between measured and desired BIS, while the second term minimizes the square of the drug injection differences in successive time steps. The problem is defined in discrete time, for all time indexes k acquiring integer values, k = 0, ..., N - 1.

It is well known that the nonlinear optimization problems are in general hard to solve. Therefore, in order to be computationally less expensive, the original nonlinear problem (8) will be reformulated into the MIQP problem, for which an efficient optimization algorithm exists and can be solved in polynomial time [19]. This can be done by replacing the nonlinear BIS equation (8e) with the approximated PWA expression given by (3). In this section, we will exploit the fact that PWA functions can be expressed as if-than-else statements, which can be directly converted into the logical propositions.

The discrete form of the PWA approximation of the BIS function (3) can be rewritten as follows

$$\delta_k^i \Leftrightarrow y_k \in \mathcal{P}^i,\tag{9a}$$

$$\delta_k^i \Rightarrow BIS_k = a_i y_k + b_i,\tag{9b}$$

where $\delta_k^i \in \{0, 1\}$, represents the binary indicator for i^{th} polyhedral partition of the PWA function in k - th time instant. Here, " \Leftrightarrow " denotes logic equivalence, i.e., the left-hand-side is true if and only if the right-hand-side is satisfied. Item " \Rightarrow " denotes logic implication, i.e., the right-hand-side is true if the left-hand-side is true. Note, that the statement (9a)

can be expressed equivalently by the following half-space representation

$$\delta_k^i \Leftrightarrow \ H_i y_k \le h_i. \tag{10}$$

However, the logical statements are not directly compatible with optimization solvers. Therefore, in the sequel we show how to reformulate the PWA expression (9) into the form which will be suitable for solution by state of the art optimization algorithms. For this purpose we will use mathematical modeling framework called a big-M method introduced by [20].

Lemma 4.1 ([20]): Consider the statement

$$[\delta = 1] \Leftrightarrow [g(v) \le 0],\tag{11}$$

where $\delta \in \{0,1\}$ is a binary variable, v is a vector of continuous variables, and $g(\cdot)$ is any function. Then (11) holds if and only if δ and v satisfy

$$g(v) \le M(1-\delta),\tag{12a}$$

$$g(v) \ge \epsilon + (m - \epsilon)\delta,$$
 (12b)

where M is a sufficiently large scalar, m is a sufficiently small scalar, and $\epsilon > 0$ is the machine precision.

Lemma 4.2 ([20]): Similarly as in Lemma 4.1 lets have the statement

$$[\delta = 1] \Rightarrow [g(v) = 0]. \tag{13}$$

Then (13) holds if and only if δ and v satisfy

$$m(1-\delta) \le g(v) \le M(1-\delta). \tag{14a}$$

Subsequently by employing Lemmas (4.1) and (4.2), the PWA function (9) expressed via logical statements can be rewritten as follows

$$H_i y_k - h_i \le M(1 - \delta_k^i), \tag{15a}$$

$$\epsilon + (m - \epsilon)\delta_k^i \le H_i y_k - h_i, \tag{15b}$$

$$m(1-\delta_k^i) \le BIS_k - a_i y_k - b_i \le M(1-\delta_k^i), \quad (15c)$$

$$\sum_{i}^{n} \delta_k^i = 1. \tag{15d}$$

The first two equations (15a) and (15b) are reformulations of the equation (9a) via Lemma (4.1). The third equation (15c) is reformulation of the equation (9b) via Lemma (4.2) and (15d) is an additional term which ensures, that only one region of the PWA function can be active at each time instant. Finally, by replacing (8e) from the original nonlinear problem in (8) by big-M model of the PWA function (15), the problem becomes MIQP which is well suited for the solution via optimization algorithms.

V. SIMULATION RESULTS

In this section, we will show the simulation results of designed hybrid MPC controller for the virtually generated patient model of age 25 years and weight 60 kg assuming the sampling time of 60 seconds. The MPC tuning parameters such as prediction horizon N was set to 10 and weighting matrices Q and R were set to 1. The following set of parameters was selected in the optimization problem (8): $0 \le u_k \le 20$, $-500 \le \Delta u_k \le 500$, $x_0 = \begin{bmatrix} 0 & 0 & 0 \end{bmatrix}^T$, $u_{-1} = 0$, and

the observer gain was obtained using discrete linear-quadratic estimator function (dlqe) of the MATLAB which is given as $L_e = [0.0275 \quad 0.0274 \quad 0.0691 \quad 0.2684 \quad 0.4908]^T$.

The hybrid MPC were implemented in YALMIP [21] and solved online using Gurobi [22] QP solvers. Designed offsetfree controller is tested for the varying BIS reference tracking, constraints handling and disturbance rejection. Upper response in Fig. 3 shows the BIS tracking response of hybrid MPC (hMPC) with and without disturbance modeling. Initially, the patient is in fully awake state i.e. BIS = 100 and then drug rate is increased to take BIS value to 50 and again optimized for varying reference. The lower response in Fig. 3 shows the optimized drug input rate for achieving desired target values. It can be observed that the drug rate obtained from the MPC controller is in given constraints but controller without offsetfree scheme has more steady state error which can be clearly seen form time 10 - 28 min.



Fig. 3. Performance of normal hybrid MPC (hMPC) (green) and offset-free hybrid MPC (blue) schemes for the control of BIS in anesthesia system.

Next, we show the complexity comparison of different MPC schemes employed in the anesthesia control. The considered controllers are as follows,

- Controller I: nonlinear MPC with and without (w/o) disturbance modeling to track BIS as an output using nonlinear PD model. This controller considers nonlinear PD model in optimization problem and solve it using fmincon solver of MATLAB.
- Controller II: hybrid MPC with and without disturbance modeling to track BIS as an output using PWA models. Here, we used Gurobi solver for optimization.

The controller complexity is compared on the basis of run-time required to complete total simulation (36 min). As computing hardware, a personal computer with an Intel Core i7 CPU with 2 GHz processor and 8 GB memory were used. As operating

system and simulation environment 64 Bit Windows 7 with MATLAB 2015b was used. Table I summarize the simulation run-time and seconds per sample taken by the optimization problem solvers employed in MPC controllers. It can be

 TABLE I.
 Run-time comparison of nonlinear and hybrid MPC

 Algorithms employed for BIS control in Anesthesia system.

MPC Controller	Time [s]	Seconds/sample [s]
Controller I: w/o offset-free	7.1662	0.1991
Controller II: w/o offset-free	1.3872	0.0385
Controller I: with offset-free	8.1146	0.2254
Controller II: with offset-free	1.7442	0.0485

observed from the table that the controllers without (w/o) offset-free scheme take less time as compared to controllers with offset-free scheme. In the run-time comparison, hybrid MPC takes less time in both the schemes (with and w/o offset-free) as compared to the nonlinear MPC as it solved the nonlinear problem of more complexity as compared to the MIQP problem in hybrid MPC. The performance of nonlinear MPC and hybrid MPC with the offset-free scheme are shown in the Fig. 4 for varying reference tracking. In many parts of the response, the performance looks like almost same but it differs in the starting of each step change which can be seen in Fig. 5.



Fig. 4. Performance of offset-free hybrid MPC (hMPC) (blue) and offset-free nonlinear MPC (NMPC) (green) strategy for BIS control in anesthesia system.

From the responses, it can be observed that the nonlinear MPC performs better but from table, it seems that hybrid MPC overperform the nonlinear MPC and it can is preferred for anesthesia control due to the less complexity and can be implemented on low-cost low-end embedded hardware.

VI. CONCLUSION

In this paper, an offset-free hybrid model predictive control scheme for closed-loop control of anesthesia using BIS as a



Fig. 5. Detailed view of the responses in Fig. 4.

clinical effect and Propofol as an anesthetic was designed and implemented in MATLAB. The nonlinear pharmacodynamic model was linearized using piecewise affine models. To deal with inter- and intra-patient variability we designed an offsetfree controller using disturbance modeling. The offset-free hybrid MPC problem was formulated as mixed integer quadratic programming problem, which was subsequently solved online using Gurobi solver. The designed controller was tested on the virtually generated patient model for BIS reference tracking. The performance and complexity of the implemented controller were compared with the nonlinear MPC strategy to achieve the same target. Results show that the offset-free hybrid MPC gives an almost same performance as nonlinear MPC and takes less time as compared to the nonlinear MPC.

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