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ORIGINAL RESEARCH

A delayed functional observer/predictor with bounded-error for depth of hypnosis monitoring

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Abstract With the motivation of providing safety for a patient under anesthesia, this paper suggests conditions for evaluating the correctness of an available user interface for systems under shared control based on observability and predictability requirements. Situation awareness is necessary for the user to make correct decisions about the inputs. In this article, we develop a technique to investigate the conditions under which an anesthetists can attain situation awareness about a limited but important aspect of anesthesia, namely depth of hypnosis (DOH). Furthermore, we consider that, in practice, to attain situation awareness, the estimation of the task states does not necessarily need to be precise but can be bounded within certain margins. Hence, attaining situation awareness about DOH is modeled as a bounded-error delayed functional observation/prediction. Unless such an observer/predictor exists for a system with a given user-interface, the safety of the operation may be compromised. The suggested technique proves that, in order to provide safety for the patient under anesthesia, it is necessary for the anesthetist to have access to the predictive information from a clinical decision support system.

Keywords Bounded-error · Functional estimator · Delayed estimator · User-modeling · Situation-awareness

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1 Introduction

We consider an anesthetist trying to monitor and control the depth of hypnosis (DOH) of a patient during an operation. For such an example, obviously, misunderstanding about the DOH and its evolution in time can result in wrong administration of the anesthetic drug, putting the patient at risk of becoming conscious and aware in the middle of the operation or going into a state of too deep hypnosis. Hence, designing a comprehensive display with carefully selected information, to provide the user with adequate understanding about the situation, is a critical step when designing an anesthesia clinical decision support system (CDSS). In fact, for any system, designing an effective display is of critical importance.

Many researchers have discussed the efficient presentation of displayed information [4, 43], however, not enough effort has been put on determining what the displayed information should be in the first place. In our previous papers, we suggested techniques based on subspace analysis [14, 16] and modeling the user [15, 18] to analyze and to design the displayed information. As in our previous papers, our approach here is based on the necessity of having situation awareness (SA) for safety of task accomplishment [10, 12, 13]. As has been mentioned by several researchers, the user of any system has to be capable of understanding the situation before processing the information, attempting to make a decision and applying a control action to the system [3, 38].

Clearly, during a surgical procedure, it is extremely important for the anesthesiologist to attain SA about the depth of hypnosis of the patient. However, precise comprehension and prediction of the information is too restrictive. In the majority of the systems in the real world the users do not require to precisely comprehend and exactly predict the task. It is generally enough, for them to make these estimations within a specific bound. Consider a driver trying to maintain the speed of a car within the speed limits. This speed limit prevents the user from exceeding a specific speed while the user should also not drive too slowly. Hence, it is important for the driver to be capable of keeping the speed within the pre-specified bounds. Similar to the example of the driver, the anesthetist also needs to make estimations and predictions of the DOH, while, these estimations/prediction do not need to be precise. In other words, it is enough for the anesthetist to make estimations within a safe bound around the actual value of DOH, e.g. assessing whether the patient is in an acceptable range of DOH for general anesthesia.

In our previous paper [15], we investigated the correctness of and then designed the displayed information for safety critical systems.The technique developed in [15] was particularly designed to verify the displays which allowed the user precisely estimate and predict the desired task, hence, it could be too restrictive to be used for the design of displays of most systems (i.e. non safety-critical systems). However, here, we model the process of attaining SA by the user as a "bounded-error" delayed functional estimator and design a tool that can be used to evaluate the displays without being too conservative.

A functional observer is an observer designed to reconstruct a specific functional of the states of the system. Several researchers have investigated different aspects of these types of observers and have designed functional observers for systems with known inputs [7, 9, 20, 21, 34, 46] and with fully or partially unknown inputs [9, 17, 19, 29, 45]. In addition, eigenspace analysis is also used to assess the existence of functional observers [30]. It is worth mentioning that the technical result in this work is an extension to our previous papers on functional observers [15, 17] which were highly inspired by [7, 21].

We consider a pharmacokinetics pharmacodynamics (PKPD) [25, 26] model of patients and our goal is to model the anesthetist as a bounded-error estimator for such a system. In general, the designed estimator is a valid one for any linear time-invariant (LTI) system with no noise and uncertainty. Since, for the systems with no uncertainty it is usually straightforward to design an observer to precisely reconstruct the states of the system [32], so far in the literature, estimators with bounded error have only been defined and designed for systems with uncertainty and/or noise [31, 36, 42, 47]. However, here our goal is to model the human rather than designing an automated observer. Further, as explained above, we believe that in many systems the human does not require to perform precise estimation of the desired states. We, therefore, need to come up with an estimator's model that makes bounded estimations of the desired states of a deterministic LTI system. More related to our objective, authors of [35, 37] have determined sufficient conditions for ϵ-convergence of functional observers, but again, the focus of these papers is on the systems affected by known or bounded unknown disturbances.

As the main contribution of this paper, we suggest a novel technique to check the boundedness of the estimation and the prediction errors of a desired functional with an estimator whose dynamics are delayed; the delay corresponding to the user processing delay. We then use this estimator to evaluate the correctness of the information available to the anesthesiologists to monitor and control DOH.

In Sect. 2 of this paper, we discuss the PKPD model—that is, the structure of the plant, and the observer/anesthetist analytically. In Sect. 3 we will introduce a Theorem and Corollary on the existence of and the type of estimator that we are looking for.

2 Problem statement

Several researchers, [23, 33, 40], have investigated the importance of attaining SA for an anesthetist to maintain the safety of the anesthetized patient. In a recent paper, [22], Fioratou et al. mention that after perceiving the available displayed information and the information from the environment, the anesthetist has to integrate all the available data for the identification of the current and the future desired patient states. The estimation of the current states of the system is important for goal accomplishment and for fault detection. In addition, according to [22], task prediction is also extremely important for the anesthetist to be proactive rather than just being reactive.

2.1 Model description

With the goal to analyze the correctness of the displayed information based on SA requirements, we model a patient under anesthesia as a delay-free system whose evolution is described by a noise-free LTI dynamics.

The first step for modeling a patient under anesthesia is to understand the relationship between the dose of the drug and its pharmacological effect. A well known model, named the PKPD model, consists of two sub-models, the pharmacokinetic (PK) and the pharmacodynamic (PD) models. The PK model, describes the effect of the administered drug on the drug plasma concentration while the PD model, describes the relationship between the drug concentration at the effect site (i.e. the brain for DOH) and the observed effect of the drug (DOH).

To model the effect of propofol administration on the depth of hypnosis we consider a simplified PKPD model described in [25, 26]. The PK model that we use is the 3-compartment model developed in [41] to evaluate the effect of propofol infusion on the drug concentration in different compartments. With a compartment being a group of tissues which have similar kinetic characteristics, a 3-compartment model has three states, i.e. concentrations in i) the blood and highly perfused tissues (e.g. the liver), ii) the muscles and viscera, and iii) fat and bones. To create the PD model, we consider the effect site concentration of the drug and linearize the Hill equation to obtain the depth of hypnosis based on this state of the system [15]. Assuming no transport delay, we use the following model for the system,

$$\dot{x}(t) = Ax(t) + Bu_h(t) + Fr_a. \tag{1}$$

with

$$A = \begin{bmatrix} A_{pk} & 0 & & \\ k_d & 0 & 0 & -k_d \end{bmatrix}, \quad B = \begin{bmatrix} B_{pk} \\ 0 \end{bmatrix}, \tag{2}$$

where

$$A_{pk} = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{12} & k_{13} \\ k_{21} & -k_{21} & 0 \\ k_{31} & 0 & -k_{31} \end{bmatrix}, \quad B_{pk} = \begin{bmatrix} V_1^{-1} \\ 0 \\ 0 \end{bmatrix}. \tag{3}$$

In (1), $u_h(t) \in \mathbb{R}^{m_b}$ is the low-level human input, controlled by the user, and $r_a \in \mathbb{R}^{m_f}$ is the reference trajectory, tracked by the automation. In this paper we consider operating conditions in which the reference trajectory is time-invariant, e.g. corresponding to the maintenance phase of anesthesia. The matrix F can be designed to make the output follow the reference trajectory. In (2) and (3), k_{ij} and k_d are rate constants and V_1 is the volume of the plasma compartment.

In real applications, the anesthetist has access to various information about each patient, including DOH, heart rate, blood pressure, SpO_2 and ECG. However, to our best knowledge, nobody has developed a patient model that can capture all these parameters. Hence, we mathematically model the output

$$y_1(t) = Cx(t), \quad y_2(t) = Dr_a, \tag{4}$$

such that it consists of two sets of measurements, (1) $y_1 \in \mathbb{R}^{p_x}$, the measured states of the system, including the DOH and probably the plasma concentration and (2) $y_2 \in \mathbb{R}^{p_r}$ the measured reference trajectory, including the desired goal of the automation. In (4), C and D matrices are of compatible sized.

Based on the theory of SA, it is necessary for the anesthetist to be able to comprehend and predict the information regarding DOH, otherwise it might not be possible for them to safely control its value [10]. In our previous paper [15], we investigated the possibility that the anesthetist could estimate the current and future DOH with complete precision and could show that by only measuring the depth of hypnosis, it would not be possible for the anesthetist to precisely predict DOH. This states that the SA cannot be precisely achieved by the anesthetist to perform a task on DOH while only having access to information about DOH. However, intuitively, the anesthetist does not require to precisely reconstruct and predict the task (i.e. reconstruction and prediction of the DOH within acceptable bound of error, e_1 and e_2, would be sufficient).

We, thus, model the anesthetist as a bounded-error delayed observer/predictor to reconstruct the functional

$$z_0(t+\tau) = Tx(t+\tau), \quad 0 \le \tau, \tag{5}$$

where τ defines the prediction horizon. Our desired task which is controlling the depth of hypnosis can be defined as $Tx = \begin{bmatrix} 0 & 0 & 0 & \gamma_h(4EC_{50})^{-1} \end{bmatrix} x$, where EC_{50} is the 50% effect concentration and γ_h is the cooperativity coefficient. For more details on EC_{50} and γ_h see [25–27].

We assume that γ derivatives of the measured states and λ derivatives of the inputs are known by the anesthetist and they use these values to make correct estimations about the task. For the sake of clarity and to omit unnecessary complications, we simply assume $\gamma \,\&\, \lambda \in \{0, 1\}$ [15]. Using a similar procedure as in Sect. 3, the reader can easily obtain the results for larger values of γ and λ. In addition, reconstruction and prediction of the desired states of the system are considered to be delayed [6, 14, 15].

According to the concepts on the data-driven (bottom-up) and goal-directed (top-down) information processing [11, 13] and also since a good user need to be capable of focusing on the task-relevant information [2, 5, 39] we consider the anesthetist to be a functional estimator rather than a full-state estimator. Hence, we assume that in order to reconstruct depth of hypnosis, the anesthetist does not put effort in estimating all observable states. Instead, they only focus on the combinations of the states whose reconstruction and prediction are necessary for the estimation of DOH. Hence, mathematically we consider the anesthetist to be a functional estimator with the goal of reconstructing and predicting the depth of hypnosis. More discussion on the reasons behind modeling the SA process as a functional estimator is provided in our previous paper [15].

2.2 Data selection

In the previous work, we assumed the anesthetist knew the precise dynamics of each patient. This, however, does not sound like a reasonable assumption. The internal estimator of the anesthetist can be considered to be formed based on a model of a nominal patient. This nominal model is the understanding of the anesthetist about an average patient in a specific category (e.g. children or adults) and is created from the real responses of various patients. In this paper, we model the human as an estimator designed based on a nominal system, we then evaluate whether the obtained model can be used to reconstruct and predict the DOH of each patient within the desired bounds.

For the patients with average response to the administered drug, the PKPD coefficients are presented in Table 1. The PK parameters are estimated from [1] and the PD values are from [28]. We randomly select two sets of coefficients in Table 1 to form the nominal model of an average-patient that the anesthetist knows internally. We then investigate the chances that with such an internal understanding about an average patient, the anesthetist can attain SA regarding the desired task within the acceptable bounds for each patient.

For our analysis, we consider two type of measurements which include (1) only the DOH [$rank(C) = 1$ and $rank(D) = 0$], (2) the DOH, the plasma concentration; although measuring the plasma concentration is beyond current state of technology; and the automation's desired trajectory [$rank(C) = 2$ and $rank(D) = 1$]. In addition, we consider three values for the prediction horizon, τ, to analyze the capability of the anesthetist to perform shorter and longer term predictions.

2.3 Generalization to LTI systems

Although, we have formulated the problem based on the requirements of our application, all the results that we obtain are valid for LTI systems of form (1) with outputs formulated in (4) and task as in (6).

As it is straightforward to design a simple feedback controller to manipulate the poles of the system, to generalize our equations we need to impose the following assumption.

Assumption 1 No poles of matrix A are placed on the imaginary axis.

In addition, in (5), the task matrix $T \in \mathbb{R}^{l \times n}$ consists of l linear combinations of the states. As in our previous papers [15, 16, 18], we formulate the task as a function $f : \mathbb{R}^l \rightarrow \mathbb{R}^s$ with s subtasks:

$$\mathcal{F} = \{x \,|\, f(Tx) \geq 0\}. \quad (6)$$

In some cases, the direct estimation of the functional $z_0(t+\tau)$ is not feasible and in order to estimate that functional, the user requires to also estimate the functional $Rx(t+\tau)$ where $R \in \mathbb{R}^{\mathcal{X} \times n}$. Hence, we introduce the extended functional as

$$z(t+\tau) = \begin{bmatrix} T \\ R \end{bmatrix} x(t+\tau), \quad (7)$$

where R is selected such that $L = [T^T, R^T]^T$ is of full row rank.

In generalization of the assumption we made about the anesthetist focusing on DOH rather than estimating all observable states, we impose the following assumption.

Assumption 2 In order to reconstruct the desired functional, the user does not estimate all observable states unless reconstructing all observable states is feasible and necessary for the estimation of the desired functional.

Detailed discussion on the human specifications and the assumptions of Sect. 2 can be found in our other paper, [15], and is thus omitted here.

2.4 Problem formulation

Now, consider the same structure for the estimator/anesthetist as in [15],

Table 1 Patients' parameters from [1, 28]

Patient	k_{10}	k_{12}	k_{13}	k_{21}	k_{31}	V_1	k_d	EC_{50}	E_0	γ
1	0.0068	0.0019	0.0007	0.0009	0.0001	20.164	1.15	3.95	93.11	1.74
2	0.0062	0.0019	0.0007	0.0009	0.0001	11.5058	1.34	4.24	92.46	1.90
3	0.0062	0.0019	0.0007	0.0009	0.0001	10.0848	10.71	5.77	91.47	1.56
4	0.0061	0.0019	0.0007	0.0009	0.0001	12.331	1.12	4.84	91.6	1.55
5	0.0065	0.0019	0.0007	0.0009	0.0001	28.0782	3.84	3.97	92.91	1.62
6	0.0062	0.0019	0.0007	0.0009	0.0001	10.7266	1.89	3.57	94.58	1.57
7	0.0062	0.0019	0.0007	0.0009	0.0001	10.5432	4.55	4.81	92.89	1.55
8	0.0059	0.0019	0.0007	0.0009	0.0001	26.8164	1.46	3.71	91.68	1.75
9	0.0062	0.0019	0.0007	0.0009	0.0001	11.5975	1.16	5.44	90.30	1.52
10	0.0063	0.0019	0.0007	0.0009	0.0001	22.44	7.41	3.60	91.38	1.82

$$\dot{\omega}(t) = N\omega(t) + J_1 Y_{0:\gamma}(t) + J_2 y_2(t) + HU_{0:\lambda}(t) \\ \hat{z}(t) = \omega(t-\tau_1) + EY_{0:\gamma}(t) \tag{8}$$

where $Y_{0:\gamma}(t)$ is the extended measured states and $U_{0:\lambda}(t)$ is the extended inputs. The estimator in (8) produces delayed and non-delayed estimations of current and upcoming values of a desired functional of states. In (8), $\omega(t) \in \mathbb{R}^{l+\mathcal{X}}$ is the state of the estimator and τ_1 is the estimation delay.

Note that in our application, $\hat{z}$ shows the understanding of the anesthetist about the states of the system, $Y_{0:\gamma}$ shows the knowledge of the anesthetist about the measured values and their derivatives, and $U_{0:\lambda}$ presents their knowledge of their own input to the system.

Analytically, the extended output vector can be written as

$$Y_{0:\gamma}(t) = O_\gamma x(t) + M_{1,0:\gamma} U_{0:\gamma}(t) + M_{2,\gamma} r_a, \tag{9}$$

where for $\gamma \in \{0,1\}$, the observability matrix $O_\gamma \in \mathbb{R}^{(\gamma+1)p_x \times n}$, a Toeplitz matrix $M_{1,0:\gamma} \in \mathbb{R}^{(\gamma+1)p_x \times (\gamma+1)p_x}$, and matrices $M_{2,\gamma} \in \mathbb{R}^{(\gamma+1)p_x \times p_r}$ and $U_{0:\gamma}(t) \in \mathbb{R}^{(\gamma+1)p_x}$ are defined as follows,

$$\begin{aligned} &O_0 = C, \quad O_1 = [C^T, A^T C^T]^T \\ &M_{1,0:0} = 0, \quad M_{1,0:1} = \begin{bmatrix} 0 & 0 \\ CB & 0 \end{bmatrix} \\ &M_{2,0} = 0, \quad M_{2,1} = \begin{bmatrix} 0 \\ CF \end{bmatrix} \\ &U_{0:0}(t) = u_h, \quad U_{0:1}(t) = [{u_h}^T(t), {\dot{u}_h}^T(t)]^T. \end{aligned} \tag{10}$$

It is desirable to determine a stable matrix N and matrices J_1, J_2, H, and E with compatible dimensions to make the estimation error remain bounded within a prespecified bounds, e_1 and e_2.

Our aim in this paper is to solve the following problem.

Problem Determine the required information for the anesthetist in order to safely anesthetize a patient.

Hence, analytically we first need to determine the following.

Subproblem Evaluate the existence of a bounded-error delayed functional observer/predictor based on the available displayed information.

3 Methodology and analytical results

Considering the anesthetists/users to be a bounded-error delayed functional estimator, we come up with a Theorem to determine the information which is necessary for them to perform their desired task safely.

From (1), (7), and (8), we have the prediction error

$$\begin{aligned} e(t) &= \hat{z}(t) - z(t+\tau) \\ &= \omega(t-\tau_1) + EY_{0:\gamma}(t) - Lx(t+\tau) \\ &= \omega(t-\tau_1) + EO_\gamma x(t) + EM_{1,0:\gamma}U_{0:\gamma}(t) + EM_{2,\gamma} r_a - Lx(t+\tau). \end{aligned} \tag{11}$$

Since in general the delay is small, for the cases that the value of prediction horizon is infinitesimal or when, in the window of prediction, the rate of changes of the input is constant with time, we can write

$$\begin{aligned} u_h(t) &= u_h(t-\tau_1) + \tau_1 \dot{u}_h(t-\tau_1), \\ u_h(t+\tau) &= u_h(t-\tau_1) + (\tau+\tau_1)\dot{u}_h(t-\tau_1) + \tau\tau_1 \ddot{u}(t-\tau_1). \end{aligned} \tag{12}$$

In [15] we showed that

$$\begin{aligned} x(t) &= e^{A\tau_1} x(t-\tau_1) + \theta_1 u(t-\tau_1) + \theta_2 \dot{u}(t-\tau_1) + \theta_3 r_a, \\ x(t+\tau) &= \eta_1 x(t-\tau_1) + \eta_2 u(t-\tau_1) + \eta_3 \dot{u}(t-\tau_1) \\ &\quad + \eta_4 \ddot{u}(t-\tau_1) + \eta_5 r_a, \end{aligned} \tag{13}$$

where

$$\begin{aligned} &\delta_1 \triangleq (e^{A\tau} - I)A^{-1}B, \\ &\delta_2 \triangleq ((e^{A\tau} - I)A^{-1} - \tau I)A^{-1}B, \\ &\delta_3 \triangleq (e^{A\tau} - I)A^{-1}F, \\ &\theta_1 \triangleq (e^{A\tau_1} - I)A^{-1}B, \\ &\theta_2 \triangleq ((e^{A\tau_1} - I)A^{-1} - \tau_1 I)A^{-1}B, \\ &\theta_3 \triangleq (e^{A\tau_1} - I)A^{-1}F, \\ &\eta_1 \triangleq e^{A(\tau+\tau_1)}, \\ &\eta_2 \triangleq \delta_3 + e^{A\tau}\theta_3, \\ &\eta_3 \triangleq \delta_1 + e^{A\tau}\theta_1, \\ &\eta_4 \triangleq \delta_2 + \tau_1\delta_1 + e^{A\tau}\theta_2, \\ &\eta_5 \triangleq \tau_1 \delta_2. \end{aligned} \tag{14}$$

Hence, under the assumption that γ and λ are selected from $\{0,1\}$, the error dynamics can be written as

$$\dot{e}(t) = Ne(t) + (NL\eta + [E \ J_1 \ K \ J_2 \ H]Q_1 - Q_2) \begin{bmatrix} x(t-\tau_1) \\ r_a \\ u(t-\tau_1) \\ \dot{u}(t-\tau_1) \\ \ddot{u}(t-\tau_1) \end{bmatrix}, \tag{15}$$

where $\eta = [\eta_1 \ \eta_2 \ \eta_3 \ \eta_4 \ \eta_5]$, $K \triangleq J_1 - NE$ and for $i \in \{1, \cdots, 5\}$, $Q_{1,i}$ and $Q_{2,i}$ are defined in (16) and (17) respectively.

In (16), $M_{1,0} = 0_{p_x \times m_b}$ and $M_{1,1} = \begin{bmatrix} 0 \\ CB \end{bmatrix}$.

Remark Having the error dynamics (15), our goal is to design the estimator matrices in (8) such that the steady-state error remains bounded for all feasible combinations of the inputs and the initial states.

We define a matrix $XU \in \mathbb{R}^{n\times i}$ which columns are selected to be all i feasible combinations of states, inputs, and input derivatives of a system, and formulate

$$Q_1 \triangleq \left[\; Q_{1,1} \;\middle|\; Q_{1,2} \;\middle|\; Q_{1,3} \;\middle|\; Q_{1,4} \;\middle|\; Q_{1,5} \;\right]$$
$$\triangleq \begin{bmatrix} O_\gamma A e^{A\tau_1} & O_\gamma(A\theta_3+F) & O_\gamma(A\theta_1+B) & O_\gamma(A\theta_2+\tau_1 B)+M_{1,\gamma} & \tau_1 M_{1,\gamma} \\ O_\gamma(I-e^{A\tau_1}) & -O_\gamma\theta_3 & -O_\gamma\theta_1 & -O_\gamma\theta_2-\tau_1 M_{1,\gamma} & 0 \\ O_\gamma e^{A\tau_1} & O_\gamma\theta_3+M_{2,\gamma} & O_\gamma\theta_1+M_{1,\gamma} & O_\gamma\theta_2+\tau_1\, M_{1,\gamma} & 0 \\ 0 & D & 0 & 0 & 0 \\ 0 & 0 & I & 0 & 0 \\ 0 & 0 & 0 & \lambda I & 0 \end{bmatrix} \tag{16}$$

$$\begin{aligned} Q_2 &\triangleq [\,Q_{2,1} \quad Q_{2,2} \quad Q_{2,3} \quad Q_{2,4} \quad Q_{2,5}\,] \\ &\triangleq [\,LA\eta_1 \quad L(A\eta_2+F) \quad L(A\eta_3+B) \quad L(A\eta_4+B(\tau+\tau_1)) \quad L(A\eta_5+B\tau\tau_1)\,] \end{aligned} \tag{17}$$

$$\begin{aligned} C_1 &\triangleq \bar{e}_1 + L\eta XU \\ C_2 &\triangleq \bar{e}_2 + L\eta XU \\ T_1 &\triangleq Q_1 XU \\ T_2 &\triangleq Q_2 XU. \end{aligned}$$

with $\bar{e}_1 = \{e_1, e_1, \cdots e_1\}$ and $\bar{e}_2 = \{e_2, e_2, \cdots e_2\}$ have i columns.

Proposition 1 *For a system of form (1) with a given feasible combinations of state-input, XU, there exists a bounded error estimator of form (8) to reconstruct the functional $z(t+\tau)$ iff there exists a random vector V, a stable N, and a matrix Z, to satisfy*

- $$T2 - NC_2 \le VT_1 \le T2 - NC_1. \tag{18}$$
- when $\tau_1 \neq 0$,
  $$N(ZT_{a,1} + VT_{b,1}) + Z(T_{a,2} - T_{a,3}) + V(T_{b,2} - T_{b,3}) = 0 \tag{19}$$

  where
  $$\begin{aligned} [T_{a,1}\; T_{a,2}\; T_{a,3}\; T_{a,4}] &\triangleq (I - T_1 T_1^{+}), \\ [T_{b,1}\; T_{b,2}\; T_{b,3}\; T_{b,4}] &\triangleq T_1 T_1^{+}. \end{aligned}$$

  and $T_{a,i}$ and $T_{b,i}$ *are of compatible dimensions.*

Proof We need to find the estimator matrices to always keep the steady-state error bounded within the desired values. With the error dynamics provided in (15) and since we consider the state-input vector to be constant, the error evolves as

$$e(t) = e^{Nt} e(0) + F_r \tag{20}$$

where the forced response, F_r, is

$$F_r = (e^{Nt} - I)N^{-1}\left(NL\eta + [E\; J_1\; K\; J_2\; H]Q_1 - Q_2\right)\begin{bmatrix} x(t-\tau_1) \\ r_a \\ u(t-\tau_1) \\ \dot{u}(t-\tau_1) \\ \ddot{u}(t-\tau_1) \end{bmatrix}.$$

Mathematically, we want the steady-state error to be bounded within pre-specified values e_1 and e_2 all the time. Considering that N will be designed to be stable, the boundedness can be formulated as

$$Ne_1 \le (Q_2 - [E\; J_1\; K\; J_2\; H]Q_1 - NL\eta)\begin{bmatrix} x(t-\tau_1) \\ r_a \\ u(t-\tau_1) \\ \dot{u}(t-\tau_1) \\ \ddot{u}(t-\tau_1) \end{bmatrix} \le Ne_2, \tag{21}$$

where $\le$ shows the element-wise inequality.

From (21) we can write

$$NC_1 \le C_T \le NC_2 \tag{22}$$

where

$$C_T \triangleq T_2 - [E\; J_1\; K\; J_2\; H]T_1. \tag{23}$$

- *Proof of* (18) Based on the methods in [8, 15, 21], since $[E\; J_1\; K\; J_2\; H]T_1 = T_2 - C_T$, the solution exists for $[E\; J_1\; K\; J_2\; H]$ if and only if

$$rank[T_1] = rank\begin{bmatrix} T_2 - C_T \\ T_1 \end{bmatrix}, \quad (24)$$

which is equivalent to saying that for the existence of a solution to $[E\ J_1\ K\ J_2\ H]$ it is necessary and sufficient that there exist a C_T such that $T_2 - C_T$ be a linear combination of the rows of T_1. Hence, $[E\ J_1\ K\ J_2\ H]$ has infinite number of solutions for arbitrary values of V where

$$C_T = T_2 - VT_1. \quad (25)$$

From (22) and (25), Condition (18) is proved and for the stability of the observer, a stable N have to exist.

- *Proof of* (19) In addition to satisfaction of (18) and stability of matrix N, it is required to choose N to satisfy $J_1 \triangleq K + NE$.
  When $\tau_1 = 0$, J_1 can be selected arbitrarily. However, when $\tau_1 \neq 0$, J_1 is not an arbitrary matrix and we need to select the triplet (N, Z, V) such that N is stable and $J_1 = K + NE$. For more discussion, see [15]. The solution to $[E\ J_1\ K\ J_2\ H]$ is as follows

$$\begin{aligned}[E\ J_1\ K\ J_2\ H] &= (T_2 - C_T)T_1^{+} + Z(I - T_1T_1^{+}) \\ &= Z(I - T_1T_1^{+}) + VT_1T_1^{+}. \end{aligned} \quad (26)$$

From (26) and the condition $J_1 = K + NE$, (19) can be achieved.

The steady-state error of the estimator will be maximized when the forced response of the error is maximum. This happens at a specific combination of N, $[E\ J_1\ K\ J_2\ H]$, states, inputs, and input derivatives. The goal here is to keep the maximum steady state error bounded.

Definition 1 The direction of xu_{max}—that is, the (input,state) vector that maximizes the error, is that of the singular-vector corresponding to the maximum singular-value of G, where G is the input-output transfer matrix of the error dynamics at a desired frequency [44].

From (15), we introduce

$$\begin{aligned} A_e &\triangleq N^* \\ B_e &\triangleq N^*L\eta + [E^*\ J_1^*\ K^*\ J_2^*\ H^*]Q_1 - Q_2 \\ C_e &\triangleq I, \end{aligned} \quad (27)$$

where N^* and $[E^*\ J_1^*\ K^*\ J_2^*\ H^*]$ are a feasible solution of the estimator matrices. Define G to be the transfer matrix representation of $(A_e, B_e, C_e, 0)$ at a desired frequency. From Definition 1, xu_{max} can be obtained as the singular-vector corresponding to the maximum-singular value of G. We can then define the following Theorem.

Theorem 1 *For a system of the form* (1)*, if there exists an estimator of form* (8) *to make bounded-error estimations of the current and/or upcoming desired functionals of the states, then the conditions in Proposition* 1 *are satisfied and for the calculated* N^*, $[E^*\ J_1{}^*\ K^*\ J_2{}^*\ H^*]$*, and* xu_{max}*, a pair* (C_T, Z) *exist to satisfy the following conditions*

1. $$\begin{aligned} &Z(I - T_{1,*}T_{1,*}{}^{+}) - C_T T_{1,*}{}^{+} + T_{2,*}T_{1,*}{}^{+} \\ &\quad - [E^*\ \ J_1{}^*\ \ K^*\ \ J_2{}^*\ \ H^*] \\ &\quad = 0 \end{aligned} \quad (28)$$

2. $$N^*C_{1,*} \le C_T \le N^*C_{2,*} \quad (29)$$

In (28) *and* (29)

$$\begin{aligned} C_{1,*} &\triangleq e_1 + L\eta xu_{max} \\ C_{2,*} &\triangleq e_2 + L\eta xu_{max} \\ T_{1,*} &\triangleq Q_1 xu_{max} \\ T_{2,*} &\triangleq Q_2 xu_{max}. \end{aligned}$$

Proof As we obtained xu_{max} to be the error-maximizing vector of a system with $[E\ J_1\ K\ J_2\ H] = [E^*\ J_1{}^*\ K^*\ J_2{}^*\ H^*]$ and $N = N^*$, Theorem 1 shows that with the obtained $[E\ J_1\ K\ J_2\ H]$ and N and with xu_{max}, still the estimation error can remain bounded (within the pre-specified values e_1 and e_2).

Note that satisfaction of (28) and (29) are not necessary for the existence of the bounded error observer due to the fact that the designed estimator from Proposition 1 is not unique. Hence, if the designed estimator in Proposition 1 does not satisfy the conditions in Theorem 1, still several other estimators may exist which can bound the maximum error of estimation.

The sufficient condition in Theorem 1 will become a necessary and sufficient condition by applying recursion, such that the calculated xu_{max} be added to the vector XU at each stage and a new estimator be designed till all conditions in Theorem 1 are satisfied. The convergence of such a recursion however remains an open issue. It is, therefore, easier to solve the conditions in the Proposition 1 and Theorem 1 simultaneously to obtain the necessary and sufficient condition.

Corollary 1 *Having matrix* XU_r *with columns randomly selected to be feasible (input,state) vectors of the process, there exist a bounded error estimator of form* (8) *to keep the estimation error within the pre-specified bounds iff the following conditions are simultaneously satisfied.*

- There exist a random vector V, a stable N, and a matrix Z, to satisfy (18) and (19) for $XU = XU_r$.
- For the corresponding N^*, $[E^*\ J_1{}^*\ K^*\ J_2{}^*\ H^*]$, and the bounded xu_{max}, there exists a pair (C_T, Zn) to satisfy (28) and (29), for $Z = Z_n$.

If the conditions in Corollary 1 are all satisfied, the estimator that gives bounded delayed estimations and predictions of the desired task exists and is not necessarily unique. Hence, among all estimators that may exist based on the nominal model, some may let the anesthetist attain SA about DOH of other patients and some may not. It is, however, not clear which of the many estimators that exist is the closest model to the internal estimator of the anesthetist. We, therefore, perform a statistical analysis to determine the chances that the anesthetist can attain SA about various patients based on different internal estimators.

4 Results and discussion

For each nominal model and each combination of the measurements and τ, we design fifty estimators; if there exists any; and then evaluate whether the designed estimator is effective to attain SA about other patients. The results are provided in Tables 2 and 3. Each table shows the chances (percentage) that the estimators designed based on a given nominal model are effective to make bounded-error estimations for other patients. As expected, the estimators designed to perform bounded error estimations for the nominal models 2 and 7 are effective to perform correct estimations for Patients 2 and 7 (respectively) all the times.

To discuss the results of Tables 2 and 3 in detail, we first clarify the difference between the selected values of the prediction horizon, $\tau = 0.5$, $\tau = 5$, and $\tau = 20$. The very short prediction horizon, $\tau = 0.5$, means that predicting a very short step ahead is desired and the explicit prediction of the states is not required for attaining SA. On the other hand, by $\tau = 5$ and $\tau = 20$ we mean that in order to attain situation awareness, the anesthetist is required to make explicit predictions 5 and 20 s in advance, respectively.

From the results obtained for $\tau = 0.5$, we can see that the estimator designed based on the nominal internal model of the anesthetist, is not necessarily capable of reconstructing and predicting the task for each individual. However, we need to notice that the possibility of making correct bounded estimations depends on the similarity between the actual and the nominal PKPD models. In addition, it can be seen that when the amount of measured information in the display is increased, it becomes less possible for the anesthetist to make correct estimations on various individuals based on the internal model. This might be due to the fact that by introducing additional measurements the internal estimator of the anesthetist is designed more specifically for the available internal nominal model. Yet this reduced accuracy of the predictions while having additional displayed information, may not hold for all combinations of the information. So, further investigation is required to examine the effect of providing the user with extra information.

For $\tau = 5$ and $\tau = 20$, when only the DOH is measured in the display, the conditions in Corollary 1 are not all satisfied. So, irrespective of the internal model of the anesthetist, the anesthetist cannot make correct bounded estimations of the task. In other words, it is never possible for the anesthetist to attain SA, even about the patient with the model being that of the internal nominal model. By increasing the information in the display, the internal estimators for the anesthetist can be designed to make correct estimations on the nominal model. For $\tau = 5$, in the majority of the cases, these internal estimators are not capable to let the anesthetist attain SA about other patients. When longer term prediction is required—that is, $\tau = 20$, the anesthetist can only attain SA about the DOH of the patient if they know the precise model of the patient.

From the results obtained in Sect. 4, regardless of the nominal model, the type of the measurements, or the definition of the prediction for SA, there is always a chance that the anesthetist cannot predict the task states within the desired bounds. Hence, a hazardous situation may occur at some point.

Because of the importance of the concept of SA in the safety of operations, and based on the results that show the existence of the cases that the anesthetist may have lack of SA about the DOH, we need to seek a way that guarantees the existence of SA for the anesthetist all the time. The solution could be providing the anesthetist with SA through a CDSS which presents predicted effect of the anesthetic drug on the patients. Two such systems are Navigator Applications Suite by GE or the SmartPilot View by

Table 2 Percentage effectiveness of the estimator designed for nominal model P2 on estimating the task for other patients

τ (s)	Rank (C)	Rank (D)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
0.5	1	0	100	100	24	100	62	90	70	98	100	30
	2	1	5	100	2.5	52.5	5	70	25	7.5	42.5	7.5
5	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	1	6	100	6	4	0	4	0	6	4	0
20	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	1	0	100	0	0	0	0	0	0	0	0

Table 3 Percentage effectiveness of the estimator designed for nominal model P7 on estimating the task for other patients

τ (sec)	Rank (C)	Rank (D)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
0.5	1	0	94	100	74	98	98	98	100	98	100	56
	2	1	0	17.5	25	17.5	0	52.5	100	0	25	0
5	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	1	0	8	2	2	4	4	100	2	2	0
20	1	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	1	0	0	0	0	0	0	100	0	0	0

Drager [24]. It is still an open issue whether with the existing uncertainties and with the differences between the PKPD models used to build these devices and the actual PKPD values of each patient, the final prediction remains in the safe bound or not. We may investigate this issue in the near future.

5 Conclusion

To evaluate the displayed information, we came up with a technique based on the SA requirements. In this technique, we considered the user as a bounded-error delayed functional estimator. For accomplishing a desired task safely, this estimator has to exist to reconstruct and predict a specific functional of the states of the system within prespecified bounds.

We used our method to investigate an important problem of safety of an anesthetized patient. Considering the anesthetist to have an internal nominal understanding about the patients, we evaluated the chances that the anesthetist will be able to attain SA about the DOH of each patient during surgery. We could show that there always exists a possibility that the anesthetist cannot attain SA about the patient's DOH—that is, the understanding of the anesthetists about the depth of hypnosis of the patient is not necessarily correct. This led us to suggest incorporating automated devices which could provide the current and the predicted values of DOH directly to the doctor.

Due to the novelty of the approach presented here, there are many directions that one can take to make the results more reliable and relevant to practice. As an example, in practice there will always be a noise introduced by the user or the device. Hence, considering the noise, nominal-model uncertainties, and uncertainties arising in the choice of design parameters such as γ and λ are necessary additions to our work. Additionally, while the PKPD model that we use in this paper only considers the effect of anesthetic drugs, it is known that the depth of anesthesia is also affected by the use of analgesics. Furthermore, we cannot ignore the effect of availability of physiological parameters such as heart rate and blood pressure in predicting DOH. Seeking a more detailed model that can capture all various information which are presented to the user and also incorporates the effect of different types of administered drugs on DOH can extensively add to the value of the results. After applying the developed technique on a more complicated and reliable model, it would be worthwhile to determine how different factors (e.g. the nominal internal model of the anesthetist) may affect the accuracy of the predictions.

In addition to the suggested future directions, determining the effect of eigenspace analysis (as in [30]) on the results of Proposition 1 can be an interesting piece of future work and may help to provide a better insight about current mathematical results.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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