

Uncertainty Minimization for Systems with Measurable Disturbance. Study case of Anesthesia-Hemodynamic Interactions*

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Abstract—In this paper, a novel control methodology is presented to regulate the complex anesthetic-hemodynamic interaction during general anesthesia by means of predictive control algorithm. The proposed framework minimizes the risk of instability arising from large uncertainty in the patient model dynamics and external disturbances such as surgical events. Identification is very difficult and only a limited amount of data can be actually used during the startup of the anesthesia as to calibrate the generic patient models. There is a crucial need to explore additional ways to minimize uncertainty in the closed loop. The paper introduces a natural mimicking strategy of actual anesthesiologists real-life decision making procedures. The framework is tested in an open access patient simulator for hypnotic drug delivery management in general anesthesia.

I. INTRODUCTION

Optimal management solutions for general anesthesia during major surgery is a challenging control task. These types of surgeries pose greater risks to patient and challenges to the anesthesiologist due to unmodelled patient dynamics: large volume shifts taking place during the operation, un-even blood perfusion, anomalous drug diffusion, synergic/antagonistic effects of intercoupled dynamic states, etc [1], [2], [3]. Additional stability issues arise from blood losses up to 1 liter, strongly affecting both hemodynamics (cardiac output, mean arterial pressure, blood pressure) as well as anesthetic states. Essentially, the drug clearance from central, blood volume compartment is not reaching its effect site due to faster and unforeseen clearance rates [4]. Very long anesthesia periods include changes in drug uptake constants and non-uniform mixing [5], [6].

The burden of predicting future patient responses is crucial in clinical practice. For instance, while the surgery is ongoing for another 10 minutes to close the incision point, the patient's state must transit to awake at minute 11-12 (open eyes and breathing on its own). The anesthesiologist must calculate and predict in real time the optimal dose to fulfil this future reference [7]. With several sensing and monitoring devices, this multivariable optimization task becomes very

complex for any human expert closing the loop [8]. Moreover, the actions depend on several individual factors such as personal expertise, stress, fatigue and patient's underlying comorbidity risks [9].

Current solutions for computer guided anesthesia management are based on limited feedback closed loop control systems, either single loop, or multi loop optimized [2], [10], [11], [12], [13], [14], and predictive control of hypnotic state [10]. Actions of the anesthesiologist have been shown to affect overall performance [7].

An original solution proposed here to overcome the bottleneck is based on a realistic mimicking context of the decision conditions of the anesthesiologist and surgeon actions. A novel methodology and control structure is hereafter introduced, allowing maximal use of information at all times during optimal input search related actions. The paper introduces hereafter the rationale for the control methodology, following supportive mathematical formulations for applying it within a predictive control algorithm. A numerical example illustrates the herein proposed solution and its added value. A section discussing the conflicting interactions in multi-loop optimization problem gives new challenges for research perspectives and points out the actual clinical needs where the proposed methodology has a potential impact. A conclusion section summarizes this work.

II. RATIONALE

Here we present a framework of operation and information flow in a predictive control context for the anesthesia-hemodynamic (AH) management problem simulator recently released in [15]. Figure 1 depicts the AH multivariable system control with 5 drug inputs (propofol, remifentanyl, atracurium, dopamine and sodium nitroprusside) and 5 measured states in the patient (hypnosis - BIS, neuromuscular blockade - NMB, analgesia - RASS, mean arterial pressure-MAP and cardiac output - CO). The disturbances from surgical stimuli and supervisory actions of the anesthesiologists are mapped as external information sources to the optimizer who uses updated patient models to predict and optimize the input according to interval constraints for patient safety.

Real World Side. In this figure, we have the patient dynamic states box where some of the dynamic states in the patient are monitored: the anesthetic states (yellow) and hemodynamic states (green). Other states include fluid management objectives, related to blood loss and respiratory rates [4], [16]. Some states such as the NMB are not coupled to the rest of the dynamics [17]. Other, unknown states refer to the unforeseen events during

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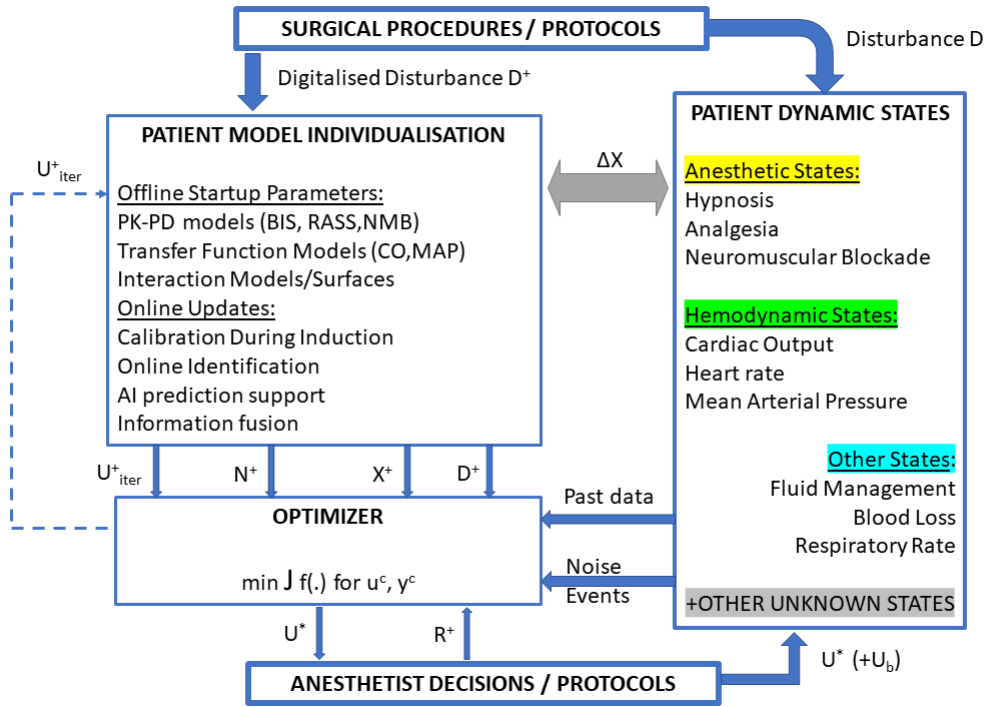


Fig. 1. Proposed framework of operation and information flow in a predictive control context for the AH management. The right part of the figure denotes the *Real World Side*, whereas the left part denotes the *Computer Side*. The amount of uncertainty among the two sides is symbolically denoted by ΔX .

surgery, e.g. risk of major perioperative cardiac events (cardiac death, atrial fibrillation, nonfatal myocardial infarct, etc) [3].

Actions of surgeon during the maintenance of AH states during surgery are perceived as disturbances in the control loop. From these, surgical procedures and protocols can be apriori digitalised in equivalent signal formulations D^+ and used as part of the disturbance model in the patient model box. An unmodelled remaining part of their effect is comprised in the disturbance signal D acting on the real patient:

$$D(t) = d^+(t) + \Delta d(t) \quad (1)$$

with $d^+(t)$ a predictable disturbance signal, and $\Delta d(t)$ the unpredictable part of the disturbance, containing unforeseen effects and events occurring in the system.

The anesthesiologist knows the surgeon's current and future actions. He can then decide and provide information to the optimizer box on the reference for AH variables through R^+ . Furthermore, he can also endorse the input solutions provided by U^* , or decide for additional bolus infusion U_b .

Computer Side. On the part of the computer, the patient model individualisation box contains two layers of information: an offline, prior to operative time computed models and an online, perioperative computed adaptations of model parameters to the patient at hand. The offline startup parameter layer is based on generic population models and biometric data from patient allowing a first characterization of the pharmacokinetic compartmental models. For example, generic transfer function models and

drug interaction models can be represented as statistical distribution maps.

The online updates of model parameter values include mainly the pharmacodynamic components, which are essentially static nonlinear gains. The induction phase of anesthesia in absence of disturbance allows identification of dynamic patient response to sequential changes in drug infusion rates of Propofol and Remifentanil for the hypnotic and analgesic PD model individualisation. Identification strategies have been proposed in [18] and validated on patient data in [19].

For surface models of gain interaction between two (or more) drugs, the computational complexity of the nonlinear sigmoid functions are beyond the practical sampling period interval (i.e. T_s around one second in clinical trial studies). A recursive method for calibrating the surface model gain of synergic drug effects between Propofol and Remifentanil has been proposed in [20]. However, if the further adaptation due to intra-patient variability (i.e. patient's response itself changes during long term induced anesthesia) then this can be performed outside the periodic sampling interval, say for instance at triggered intervals based on events, T_e denoting an aperiodic sampling interval [21]. Recent studies from intensive care clinical data analysis claim that artificial intelligence based prediction models can add to the model prediction information through fusion of several variables [22]. The purpose of the online model update layer is to minimize the uncertainty in model parameters by minimizing the difference ΔX between the predicted and the actual states.

The patient model and optimizer box communicate

through exchange of predicted patient response X^+ , predicted surgical actions D^+ , disturbance prediction models N^+ and iteratively computed optimized input set of actions in drug rate updates U_{iter}^+ . The optimizer box minimizes the cost function with respect to input u^c and possibly output y^c constraints and delivers an optimal input set U^* . The optimizer uses information from the actual patient from monitored variables, past inputs and noise and events captured in these monitored variables. Notice that in this control problem, not all monitored variables are direct measures of AH states, i.e. some of the controlled variables denote indirect measures of actual states.

III. MATHEMATICAL FORMULATIONS

Consider a system y described by:

$$y(t) = f(t, d, y, n, x, \dots) + b \cdot u(t) \quad (2)$$

where b is a gain for the input u and $f(\cdot)$ is a nonlinear function representing the time-variant system, disturbances d , model x including uncertainties, noise n etc. For additive exogenous disturbance we have that

$$\dot{x}_R(t) = f(x_R(t), u(t)) + n(t), \quad n(t) \in D \quad (3)$$

where $x_R(t) \in \mathfrak{R}$ denotes the real system states and $u(t) \in \mathfrak{R}$ the control input at time instant t . The disturbances of this system are represented by $n(t) \in D \in \mathfrak{R}$ are assumed to be bounded and finite. The system is subject to control constraints $u(t) \in U \in \mathfrak{R}$ a compact set including zero conditions. Nominal dynamics of the unconstrained system without disturbance are defined by

$$\dot{x}(t) = f(x(t), u(t)) \quad (4)$$

Model predictive control formulation implies optimizing a cost function

$$\min_u J(x(t), u(\cdot)) \quad (5)$$

subject to

$$\begin{aligned} \dot{x}(t^+, x(t)) &= f(x(t^+, x(t)), u(t^+)), \\ x(t, x(t)) &= x(t) \\ u(t^+) &\in U, \quad t^+ \in [t, t + N_p] \\ x(t + N_p, x(t)) &\in X \end{aligned} \quad (6)$$

where the cost function may contain both error and control effort terms, adequately normalized. Notice in this formulation, the nominal model from (4) is used as the prediction model of the real system from (2), without disturbance prediction. The notation t^+ denotes prediction variables over the time interval defined by the prediction horizon N_p , and the predicted state $x(\cdot, x(t))$ denotes the base prediction of the process model for the control law $u(\cdot)$. We denote the optimal value as $J^0(x(t))$ and assume that the optimization problem is feasible at initial time instant. In this formulation, one can guarantee robust stability for the system for any disturbance n below a maximal bounded norm value if the system's states are measurable [23]. Following the MPC receding horizon principle, the optimization problem will be solved repeatedly at every new measurements available

instants. This can be either periodic sampled at T_s seconds, or aperiodic event-based sampled at T_e seconds. For all disturbances defined by $\Delta d(t)$ bounded and decaying for the prediction horizon N_p , we can guarantee the system is asymptotically stable [23], [24]. Under the assumption that a minimum solution can be found at all times, for any $t^+ \in [t, t + N_p]$,

$$u^*(t^+, x(t)) := \arg \min_{u(\cdot) \in U} J(x(t), u(t^+)) \quad (7)$$

and the applied control is $u^*(t^+, x(t))$, for $t^+ \in [t, t + T_s]$.

As proven in [23], linear systems with pseudo-infinite horizon MPC and bounded disturbances, are input-to-state stable. For the nominal system defined by:

$$\dot{x}(t) = f(x(t), u(t)) + n(t) \quad (8)$$

the total noise comprises the disturbance signal from (1):

$$n(t) = F \cdot e(t) + d^+(t) + \Delta d(t) + \Delta x(t) \quad (9)$$

with F a disturbance filter containing at least one integrator to ensure zero steady state error and $e(t)$ denoting white noise. The terms $\Delta d(t)$ and $\Delta x(t)$ denote remaining unmodelled disturbance and unmodelled dynamics, respectively. All signals may be subject to stochastic noise, not explicitly formulated. When (8) is used as prediction model, the measured output $y(t)$ from (2) contains both uncertainty and noise components. However, only the terms $\Delta d(t)$ and $\Delta x(t)$ from (9) remain unknown, albeit possibly estimated.

In the study case context presented in this paper, we shall focus on signal representation only. The initial conditions of the system nominal model allow a guaranteed stability solution for the optimal input in absence of disturbance $D(t)$ - i.e. the induction phase of general anesthesia. Furthermore, in the proposed online execution paradigm the term $\Delta x(t) \rightarrow 0$ as the system model is recursively identified throughout the induction phase and in the maintenance phase for those time intervals where $d^+(t) = 0$.

The remaining $\Delta d(t)$ term from (1) will contain mainly stochastic noise and unforeseen events acting as a disturbance for the real system. Observer based compartmental model to account for unforeseen events such as blood loss [16] can be used to monitor effects of unforeseen events on the nominal system dynamics $x(t + N_p, x(t)) \in X$ from (6).

IV. EXAMPLE

In [7] we showed that the effects of the anesthesiologists actions affect the performance in hypnosis regulation. This was tested by adding in the optimal control value in (7) additional manual bolus infusion U_b . Although this extra bolus is not available in the optimizer as future action, once applied, it becomes part of the actual input and becomes available to the optimizer as past control action to the system. Here we present the same process for regulating hypnosis, with input load disturbance coming from the actions of the surgeon on the patient. No constraints are imposed and no real clinical values simulated for reference or disturbance

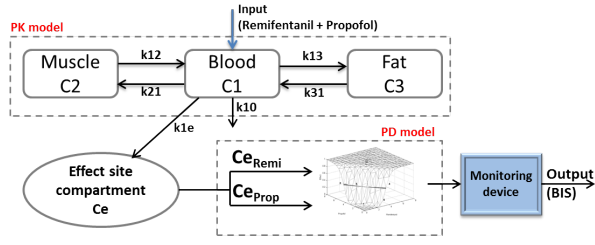


Fig. 2. A schematic representation of a compartmental model for PK and PD with two inputs and one output. For the purpose of this paper, only one input (Propofol) has been considered active and the second one (Remifentanyl) is zero.

amplitudes. A generic schematic representation of a PK-PD compartmental model is presented in Figure 2.

The Propofol uptake as a pharmacokinetic (PK) model are given by the relations to the variation of concentrations c_i within $i = 1..3$ the respective compartments (i.e. blood, muscle, fat):

$$\begin{aligned} \dot{c}_1(t) &= k_{12}c_2(t) - k_{13}c_1(t) - k_{10}c_1(t) - \\ &\quad k_{1e}c_1(t) - k_{21}c_1(t) + k_{31}c_3(t) + u(t)/V_1 \\ \dot{c}_2(t) &= k_{21}c_1(t) - k_{12}c_2(t) \\ \dot{c}_3(t) &= k_{13}c_1(t) - k_{31}c_3(t) \end{aligned} \quad (10)$$

with $u(t)$ the input infusion rate of drug (Propofol, Remifentanyl, or a combination of both to achieve desired hypnotic state measured by BIS variable) and where the parameters k_{ji} for $i \neq j$, denoting the drug transfer frequency from the j^{th} to the i^{th} compartment and $u(t)$ [mg/s] the infusion rate of the anaesthetic drug into the central compartment. An additional hypothetical effect compartment represents the lag between drug plasma concentration and drug response:

$$\dot{c}_e(t) = k_{1e}c_1(t) - k_{e0}c_e(t) \quad (11)$$

The coefficients of the PK model [1/min] can be calculated from age, weight, height, gender and generic compartmental volumes [l] and clearance rates [l/min]:

$$k_{10} = \frac{C_{l1}}{V_1}; k_{12} = \frac{C_{l2}}{V_1}; k_{13} = \frac{C_{l3}}{V_1}; \quad (12)$$

$$k_{21} = \frac{C_{l2}}{V_2}; k_{31} = \frac{C_{l3}}{V_3}; k_{e0} = 0.456; \quad (13)$$

The clearance rates are:

$$\begin{aligned} C_{l1} &= 1.89 + 0.0456(\text{weight} - 77) - \\ &\quad -0.0681(\text{lbm} - 59) + 0.0264(\text{height} - 177) \\ C_{l2} &= 1.29 - 0.024(\text{age} - 53); C_{l3} = 0.836 \end{aligned} \quad (14)$$

where lbm - lean body mass, calculated as:

$$lbm_{men} = 1.1 \cdot \text{weight} - 128 \cdot \frac{\text{weight}^2}{\text{height}^2} \quad (15)$$

For the Propofol infusion rate, these volumes $V_1 = 4.27$, $V_2 = 18.9 - 0.391 \cdot (\text{age} - 53)$ and $V_3 = 2.38$ for blood, muscle and fat, respectively.

The relation between the effect site concentration and the measured effect in the brain, i.e. the Bispectral Index (BIS)

is modelled as a nonlinear sigmoid Hill curve scaled between 0%-100%, with 100% denoting fully awake patient:

$$BIS(t) = E_0 - E_{max} \frac{c_e^\gamma(t)}{c_e^\gamma(t) + c_{50}^\gamma} \quad (16)$$

where E_0 is the BIS value when the patient is awake; E_{max} is the maximum effect that can be achieved by the infusion of Propofol; c_{50} is the Propofol concentration at half of the maximum effect and γ is a parameter which together with the c_{50} determines the patient sensitivity to the drug. E_0 and E_{max} are considered equal to the value of 100. An in-depth analysis of patient sensitivity has been published in [18]. In this example the gain interval is scaled within [0,1].

TABLE I

REPRESENTATIVE PATIENT DATABASE (ALL MALES) WITH PK MODEL BIOMETRIC VALUES AND PD MODEL SENSITIVITY VALUES FROM [15].

Index	Age (yrs)	Height (cm)	Weight (kg)	c_{50} (mg/ml)	γ
1	74	164	88	2.5	3
2	67	161	69	4.6	2
3	75	176	101	5	1.6
4	69	173	97	1.8	2.5
5	45	171	64	6.8	1.78
6	57	182	80	2.7	2.8
7	74	155	55	1.7	3.5
8	71	172	78	7.8	2.9
9	65	176	77	2.9	1.88
10	72	192	73	3.9	3.1
11	69	168	84	2.3	3.1
12	60	190	92	4.8	2.1
13	61	177	81	2.5	3
14	54	173	86	2.5	3
15	71	172	83	4.3	1.9
16	53	186	114	2.7	1.6
17	72	162	87	4.5	2.9
18	61	182	93	2.7	1.78
19	70	167	77	6.8	3.1
20	69	168	82	9.8	1.6
21	69	158	81	3.2	2.1
22	60	165	85	5.1	2.51
23	70	173	69	3.67	3.1
24	56	186	99	5.8	2.3

Two cases are simulated: i) when the disturbance is unknown and ii) when the disturbance is known at the time instant t . The results are given in Figures 3 and 4, respectively. A statistical analysis on the relative error calculated as:

$$Error = \frac{\sum_1^{N_s} (R(t) - Y(t))^2}{\sum_1^{N_s} U^*(t)^2} \quad (17)$$

with $N_s = 1000$ the total number of simulated samples, $R(t) = -1$ the reference, $Y(t)$ the process output variable and $U^*(t)$ the controller input variable to the process. A statistically significant difference has not been observed when Anova test was performed ($p < 0.25$), and Figure 5 gives the boxplot where a decrease of about 30-40% in the error value distribution is observed for the case when disturbance is measured.

Limitations of this example are that effects of uncertainties in the amplitude or time of occurrence of the disturbance profile are not investigated here. Additional effects of blood

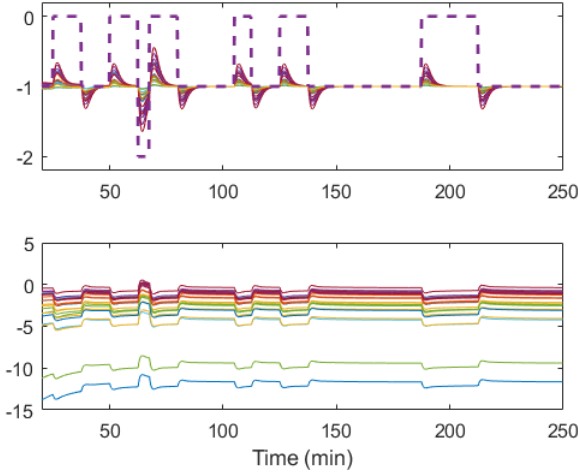


Fig. 3. Closed loop performance with unknown disturbance profile (dashed line) for all patients from Table I. Y-axes normalized values (unitless). Top plot BIS values; bottom plot propofol infusion rates.

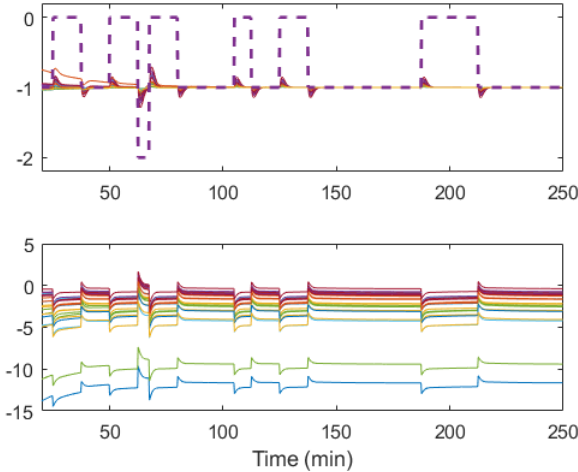


Fig. 4. Closed loop performance with measured disturbance profile (dashed line) for all patients from Table I. Y-axes normalized values (unitless). Top plot BIS values; bottom plot propofol infusion rates.

loss introducing further uncertainty in the patient model predictions are not considered.

V. CONFLICTING INTERACTIONS

The AH regulatory framework for computer based control of drug infusion rates is a complex problem, with challenging interactions in the multi-system dynamics [1], [4], [25]. In [15], both synergic and antagonistic dynamic interactions are included, making it a globally very difficult problem for the control optimizer unit. It is of paramount importance to give reliable information on model and signal flow in this multivariable system, as to fully exploit the benefits of predictive control. The AH dynamic interactions can be monitored as an input-output effect, overviewed in Table II. In this table, the synergic effects of two or more drugs are not explicitly mentioned, but they are present; e.g. the two

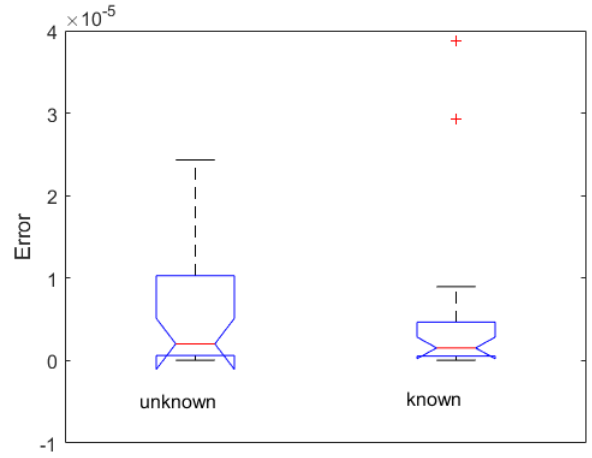


Fig. 5. Anova boxplot representation of the error calculated with (17) for the two cases: unknown disturbance (left column) and measured disturbance (right column). In this figure, per group, we have the median value (red line), the edges of the box are the 25th and 75th percentiles, the whiskers extend to the most extreme datapoints the algorithm considers to be not outliers, and the outliers are plotted individually (1.5 times away from median).

inputs Propofol and Remifentaniil have synergic effect on the BIS output variable.

TABLE II

CROSS EFFECTS BETWEEN INPUTS AND OUTPUTS FOR THE AH MULTIVARIABLE SYSTEM, AS DESCRIBED IN [15]. THE EFFECTS ARE CHARACTERIZED BY AN INCREASE (+) OR A DECREASE (-) IN THEIR VALUES. CHANGES BASED ON A POSITIVE STEP CHANGE IN THE CORRESPONDING INPUT.

	BIS	RASS	NMB	CO	MAP	HR
Propofol	-			-	--	+
Remifentaniil	-	--	-	+	-	-
Atracurium			--			
Dopamine	+			++	+	+
SNP	+			+	+	-

The AH simulator features also cross effects between output variables, as listed in Table III. For instance, an increased cardiac output will faster clear the drug from the blood compartment, increasing the BIS values.

Practical limitations. All drugs have high related costs and serious side effects; some drug cocktails have synergic (higher than merely cumulative) effects and others have antagonistic (blocking, reducing, opposite) effects. Reaching optimal dosage is challenging due to the large scale and complexity of the problem and it is critical for ensuring patient safety, minimize complications and post-interventional risks while aiming to provide best-of-care.

Blood loss compartments and observer based state estimators [16] to account for effects on the patient model (i.e. affects time constants) are not included in this study, nor in the AH simulator published in [15]. These effects are important in major vascular surgery to ensure good closed loop performance and stability.

Noticeable, a human being/patient is not a typical test-

TABLE III

AN OVERVIEW OF CROSS EFFECTS BETWEEN OUTPUT VARIABLES. THE EFFECTS ARE CHARACTERIZED BY AN INCREASE (+) OR A DECREASE(-) IN THEIR VALUES FOR A POSITIVE STEP CHANGE IN THE CORRESPONDING OUTPUT.

	BIS	RASS	NMB	CO	MAP
BIS		+		+	+
RASS	+			+	+
NMB					
CO	+	-	-		+
MAP	+			+	

bench used in systems and control engineering; i.e. strong limitations arise in the ability to apply persistent excitation in drug infusion profiles to perform identification for modelling, prediction and optimal control design. In manual control, the quality of clinical decision varies also with anesthesiologist's personal opinion, degree of expertise (i.e. beginners will tend to over-dose) and work factors (stress, fatigue, anxiety).

Opportunities. Many surgical procedures have explicit intervals of definite actions, including risk mitigation and alarm procedures for critical situations. All this information can be implemented apriori (e.g. protocol digitalisation) as proposed here, but could benefit from online learning mechanisms with artificial intelligence tools (reinforcement learning seems to be a good candidate but requires explorative research) [22]. Human endorsement must be included as a supervisory shell on top of the control system hierarchy, with low level/high level risk decisions – the coding could be as simple as a Boolean variable, or yes/no queries.

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