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Automatic Regulation of Anesthesia via Ultra-Local Model Control

Eleonora Manzoni * **Mirco Rampazzo** *

* *Department of Information Engineering, University of Padova, via Gradenigo 6/B, I-35131 Padova, Italy. e-mail: eleonora.manzoni@phd.unipd.it, mirco.rampazzo@unipd.it*

Abstract: As a part of the BMS2021 Benchmark Challenge, this paper deals with the design and testing of a closed-loop anesthesia delivery regulation system by exploiting the open-source Matlab-based patient simulator. Because of system inherent complexity together with intra- and inter-patient parameters variability and partially unknown disturbances, traditional model-based approaches may suffer. To overcome these limitations, we opt for a data-driven approach using real-time ultra-local models coupled with the corresponding so-called intelligent controllers. In this way, one maintains the hemodynamic variables while regulating the levels of hypnosis, analgesia, and neuromuscular blockade in anesthesia by automatic delivery of drugs. The performance of the proposed approach has been evaluated in silico by considering a representative dataset composed of 24 patients, the presence of disturbances mimicking both surgical stimulations and actions of "anesthesiologist in the loop", including also noise effects and time-varying system delays.

Keywords: Anesthesia, Ultra-local model, Intelligent PID, Control, Simulation.

1. INTRODUCTION

In the Health 4.0 era, technologies such as automation, robotics, sensors, IoT, cloud computing, Big Data, artificial intelligence, etc., are bringing a major change in the healthcare industry, Aceto et al. (2020), Ghita et al. (2020). In this scenario, modelling and simulation tools offer new possibilities to dominate the complexity of certain biomedical applications and they enable to accelerate innovation cycles, rapidly exploring and exploiting new possible solutions. In particular, advanced control systems play an important role in the bioengineering sector and it is a common practice to design control algorithms in silico, exploiting models that allow simulating the main relevant system characteristics for the first assessment of different control strategies. In the aforementioned context, as part of the 11th IFAC Symposium on Biological and Medical Systems (BMS2021), the benchmark challenge for the optimization of anesthetic and hemodynamic drug delivery problem in an open-source simulated patient environment enables the possibility of working on a relevant and complex medical application, Ionescu et al. (2021). The main goal is to maintain the hemodynamic variables while ensuring a suitable level of depth of anesthesia. Due to the intrinsic system complexity arising from multi-inputs and multi-outputs, non-linearities, noise effects, delays, and coupling effects, the design of suitable control systems is a non-trivial task. Promising approaches have been proposed in the literature to face this problem ranging from PID control, Padula et al. (2017), to Model Predictive Control, Ionescu et al. (2021), including Adaptive Control, Nino et al. (2009). Most of these methods heavily rely on a priori models that usually are difficult to calibrate and whose parameters depend on intra- and inter-patient variabilities. Moreover, the presence of uncertainties and disturbances may reduce the control performance. To overcome these limitations, this paper presents the use of a data-driven control approach that does not require a priori knowledge of the system behaviour, which has been proposed by Fliess and Join (2013). The approach considers a general structure for an unknown system using input-output measurements to estimate unknown dynamics using ultra-local models in an online fashion and then to generate suitable control policies. The method has been successfully applied to several control applications ranging from transportation systems, Menhour et al. (2013) to refrigeration systems, Rampazzo et al. (2017), including biomedical systems, Bara et al. (2018). On the other hand, the availability of a model remains nevertheless irreplaceable at this stage for control design and test tasks. By exploiting the Open-source Virtual Patient Simulator, we design and test a MIMO ultra-local model controller to maintain the Mean Aortic Pressure (MAP) and the Cardiac Output (CO) while regulating the level of depth of anesthesia. In particular, the controller manipulates drugs infusions i.e. Propofol, Remifentanil, and Atracurium to regulate the Bispectral Index Scale (BIS), the Ramsay Agitation Score (RASS), and the Neuromuscular Blockade (NMB). The performance of the employed straightforward approach is evaluated in simulations by considering a representative dataset composed of 24 patients, noise effects, the presence of disturbances mimicking both surgical stimulations and actions of "anesthesiologist in the loop" including also time-varying system delays. The paper is organized as follows: Section 2 depicts the Patient Simulator; the ultra-local model control is presented in Section 3; Section 4 shows simulation results in several operating conditions; some concluding remarks are given in Section 5.

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2. THE OPEN-SOURCE PATIENT SIMULATOR

The Matlab-based open-source Patient Simulator comprises, within its features, complex synergic and antagonistic interaction aspects between general anesthesia, i.e. sedation, and hemodynamic variables. The first includes hypnosis, analgesia, and neuromuscular blockade states, while the latter includes cardiac output and mean arterial pressure. The simulator includes a representative patient dataset (24 patients with different ages, heights, weights, etc.) and it can be profitably used for designing and testing control algorithms. In particular, there is the possibility to take into account up to 5 manipulated drug dosing rates variables (i.e. Propofol, Remifentanil, Atracurium, Dopamine, and Sodium Nitroprusside SNP) and up to 5 direct controlled variables (i.e. BIS, RASS, NMB, CO, and MAP), along with numerous non-linear interaction effects. The dose-effect response in the model is given by a nonlinear Hill equation, which relates values of the drug concentration profile with values of its effect. However, as shown in Ionescu et al. (2015), during the maintenance phase, the nonlinear Hill curve sigmoidicity reduces to linear parameter dependence. The presence of surgical stimulation, such as the arousal due to laryngoscopy, intubation, incisions, periods of no stimulations, and total stimulation withdrawing, lays to a nociceptor stimulation; this stimulation is optionally mimicked in the simulator as a disturbance at the output of the hypnotic state, i.e. added to the BIS value. There is also the possibility to enhance the realism of the scenario taking into account the "anesthesiologist in the loop" effect; with the manual intervention of the anaesthesiologist an additional input signal, in form of drug boluses, is delivered to the system as an anticipatory action of the anaesthesiologist itself to partially compensate the expected disturbance profile, Copot and Ionescu (2018). Another challenge for control design is the presence of time delay in the BIS output since BIS-controlled systems rely on the epoch-based estimation of EEG time windows, Ionescu et al. (2010). Indeed, in common practice, the quality of the epoch portions of EEG signal is monitored through a signal quality index. If for an epoch the value of the quality index is below a threshold limit, then the current EEG window interval is discarded, and the BIS value from the previous valid window evaluation is provided as hypnotic level output. This introduces a time delay that may vary between 10-240 seconds. In the simulator, one can choose to have a delay-free BIS signal, or a constant delay value of 30 seconds, or a variable time delay within the given interval. The presence of this time delay on the BIS signal might cause a significant decrement in the overall control system performance. Further details of the patient simulator for the design and the evaluation of drug dosing control in anesthesia can be found in Ionescu et al. (2021).

3. ULTRA-LOCAL MODEL CONTROL

Unlike a priori global first-principle model-based approaches, the ultra-local model is an affine dynamic model that involves the output y, a lumped unknown nonlinear function F, the input u, and an input gain α. To put it simply, let us consider a SISO causal system, whose dynamic is nonlinear and affected by uncertainties. In this scenario, the following phenomenological Ultra-Local Model (ULM) describes the system behaviour in a suitable short time interval T_s:

$$\dot{y}(t) = F(t) + \alpha u(t), \tag{1}$$

where the order of output derivative equals 1. In (1), F contains all system structural information and it encompasses not only the unknown system structure but also the disturbances; indeed, F depends on the initial conditions and the unavoidable disturbances, and it can be estimated via input and output measurements. Moreover, the gain α is a non-physical parameter, which is typically chosen such that $\dot{y}$ and αu are of the same magnitude.

To regulate the system output y, the ultra-local model controller, also known as intelligent PID controller, Fliess and Join (2009), can be straightforwardly designed as follows:

$$u(t) = \alpha^{-1}\left[\dot{r}(t) - \hat{F}(t) + \mathcal{C}(e(t))\right], \tag{2}$$

where $r(t)$ is the output reference trajectory, $\hat{F}(t)$ is a real-time estimate of F, while $e(t) = r(t) - y(t)$ is the tracking error. If $\hat{F}$ is satisfactory, then by combining (1) and (2), one obtains:

$$\dot{e}(t) + \mathcal{C}(e(t)) = \hat{F}(t) - F(t) \approx 0, \tag{3}$$

where the unknown system structure and disturbances vanish. The controller $\mathcal{C}$ is then chosen to ensure asymptotic stability, e.g. one can use a standard proportional controller as follows:

$$\mathcal{C}(e(t)) = K_p e(t), \quad K_p > 0, \tag{4}$$

obtaining the so-called ULM-iP, also known as Intelligent P controller. It is worth noticing that, $\hat{F}(t) - F(t)$ in (3) can be viewed as an additive disturbance.

3.1 Estimation of $\dot{y}$ and F

The employed control architecture leverages the estimation of both $\dot{y}$ and F. Given the measure of y, then $\hat{\dot{y}}$ can be inferred through the feedback scheme depicted in Fig. 1 where the integrator output has to track the reference y. Indeed, the integrator input can be regarded as an estimate for $\dot{y}$. In particular, a Robust Exact Differentiator (RED) scheme is used, Levant (1998), employing the so-called super-twisting algorithm:

$$\begin{cases} \hat{\dot{y}} = z - a\sqrt{|\xi|}\ \mathrm{sign}(\xi), \\ \dot{z} = -b\ \mathrm{sign}(\xi). \end{cases} \tag{5}$$

where z is an auxiliary variable, whereas a and b are positive constants. The reference error ξ, as well as its first time-derivative, are forced to zero in finite time. Once $\hat{\dot{y}}$ is available, then $\hat{F}$ can be computed from (1) as follows:

$$\hat{F} = \hat{\dot{y}} - \alpha\tilde{u}, \tag{6}$$

where $\tilde{u}$ is an approximate value of u and it is chosen to avoid algebraic loops: e.g. it can be set to the value of the manipulated variable in the last time step, i.e. $\tilde{u}(t) = u(t-T_s)$.

3.2 Time-delayed and MIMO Systems

Time-lag. If there is a shift in the effect of input on output dynamic response, i.e. a delay L affects the system,

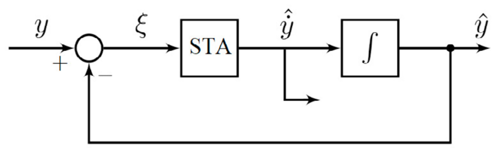


Fig. 1. Robust exact differentiator (RED) scheme.

the ultra-local model control may also be applied to regulate the output by replacing (1) with:

$$\dot{y}(t) = F(t) + \alpha u(t - L). \tag{7}$$

MIMO. The ultra-local model control may also be extended to regulate a $n \times n$ MIMO system where inputs $u_1, u_2, \ldots, u_n$ and outputs $y_1, y_2, \ldots, y_n$ turn out to be naturally decoupled in n mono variable systems of type (1). Therefore, n ULM-iP controllers, each of which has the form of (2), are used. It is worth highlighting that, for the i-th ULM-iP, $\hat{F}_i$ is not necessarily independent of the inputs $u_1, \ldots, u_{i-1}, u_{i+1}, \ldots, u_n$.

4. NUMERICAL SIMULATIONS

The ultra-local model control (2)-(4) can be regarded as a feed-forward control based on the local model in combination with a standard proportional controller Fig. 2. The overall goal is to regulate BIS, RASS, and NMB within the clinical intervals by manipulating Propofol, Remifentanil, and Atracurium drugs infusion respectively, ensuring a suitable level of depth of anesthesia, while maintaining hemodynamic variables within the clinical intervals. Moreover, the minimum and maximum values for the inputs and outputs are as follows: BIS interval [40,60]%, RASS score [-4,-5], NMB [0,100]%, Propofol infusion [0,5]mgkg^{-1}min^{-1}, Remifentanil infusion [0,2.5]mcgkg^{-1}min^{-1}, Atracurium infusion [0,10]mcgkg^{-1}min^{-1}. The CO and MAP have to be maintained within the intervals [4,6.5]lmin^{-1} and [65,110]mmHg, respectively.

In the following simulation examples, by taking advantage of the Patient Simulator as a tool to design and asses control strategies, the ULM-iP control has been tuned through trial and error procedures to ensure stability and performance, Fliess and Join (2014), during both the induction and maintenance phases of anesthesia. In particular, the performance of the proposed approach

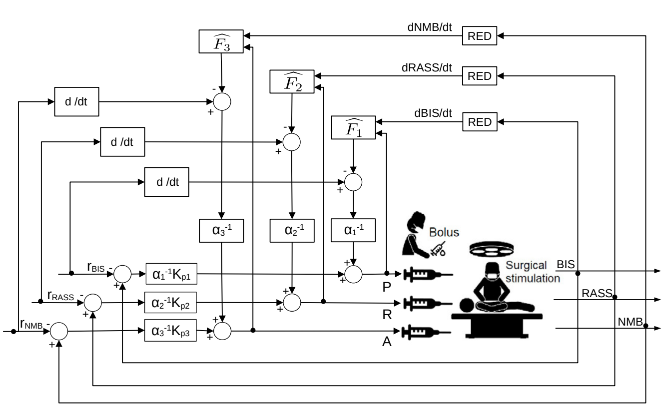


Fig. 2. ULM-iP control architecture.

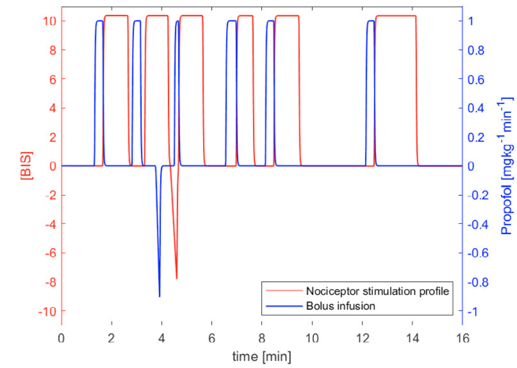


Fig. 3. The nociceptor stimulation profile and additional bolus infusion as anticipatory action of the anesthesiologist.

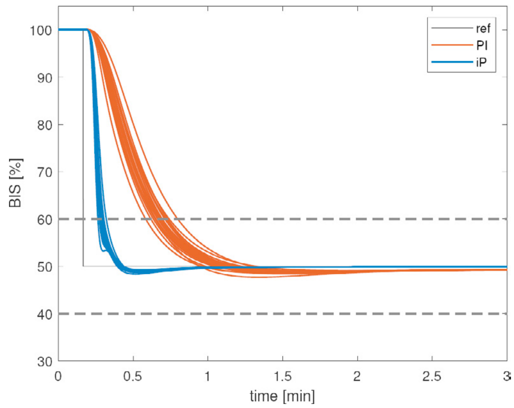
is evaluated by considering the representative dataset composed of 24 patients, and the presence of disturbances mimicking both surgical stimulations and the actions of “anesthesiologist in the loop”, Fig. 3.

4.1 SISO Examples: Propofol-BIS

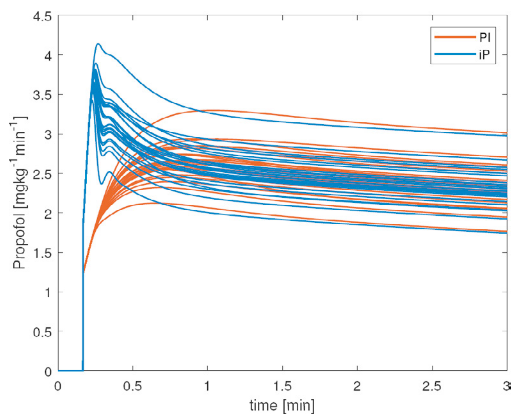
I) In this simulation example, the controller has to maintain the depth of hypnosis at $r_{BIS} = 50\%$ by acting on Propofol infusion, assuming that the delay affecting the Propofol-BIS interaction is negligible. We compare the performance of the ULM-iP control (i.e. $\mathcal{C}(e(t)) = K_p e(t)$) and standard Porportional-Integral (PI) controller (these two controllers are equivalent in some sense). Figs. 4a, 4b, and 4c, depict BIS, Propofol infusion, and the Integral Time Squared Error (ITSE) over the time, respectively, for both controllers, during the induction phases, related to the 24 patients. The ULM-iP and PI controllers have been fairly tuned so that they exhibit the same magnitude of overshoots. The ULM-iP control responses are faster than the standard PI; moreover, the ULM-iP control compensates the intra- and inter-patient variations aligning the BIS responses, Fig. 4a, not exceeding the input constraints Fig. 4b, while ensuring satisfactory performance in terms of ITSE mean and standard deviation, Fig. 4c. Fig. 5 shows the $\hat{F}$ over the time related to the 24 patients. The PI standard regulator is characterized by K_p=0.025mgkg^{-1}min^{-1}%$^{-1}$ and K_i =0.0025mgkg^{-1}min^{-1}%$^{-1}$s^{-1}, while the ULM-iP controller has parameters α= -1500%s^{-1}kgminmg^{-1} and $K_p = -0.3$mgkg^{-1}min^{-1}%$^{-1}$.

Figs. 6a, 6b, and 6c depict the performance of both ULM-iP control and standard PI during the maintenance phase under the influence of both surgical disturbance and anesthesiologist action, like those shown in Fig. 3. The ULM-iP control gives the best performance; indeed it maintains the BIS within the admissible intervals while guaranteeing good performance in terms of quick disturbance rejections and ITSE.

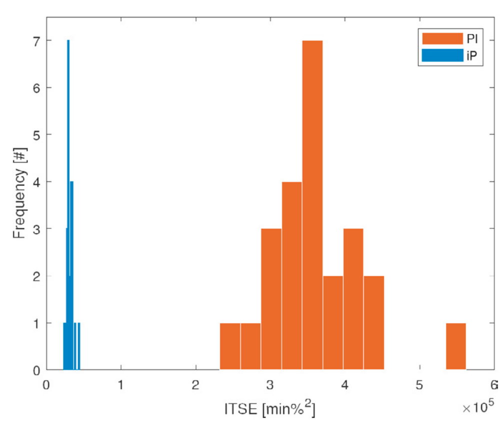
II) In clinical practice, the BIS signal is affected by measurement noise that can be modelled as an additive white Gaussian noise, with zero mean value and a suitable standard deviation. In this simulation example, the BIS is affected by an additive noise with standard deviation equals 6.27%, Padula et al. (2017). Figs. 7 depict the



(a) BIS regulation.



(b) Propofol infusion.



(c) Control performance: ITSE.

Fig. 4. BIS controlled by Propofol manipulation during induction phase (24 patients): ULM-iP (blue) vs PI (orange).

behaviour of both PI and ULM-iP controller. It is evident that, even in this case, the performance of the ULM-iP is better than that of standard PI, Fig. 7a, also thanks to the presence of the intrinsic ULM-iP feed-forward action, Fig. 7b.

III) For example purposes only, a uniformly distributed random time-varying delay $\in [0,30]$s is taken into account over the 24 patients during induction and maintenance phases simulations, Fig. 8. The satisfactory behaviour and performance of the ULM-iP controller are depicted in Figs.

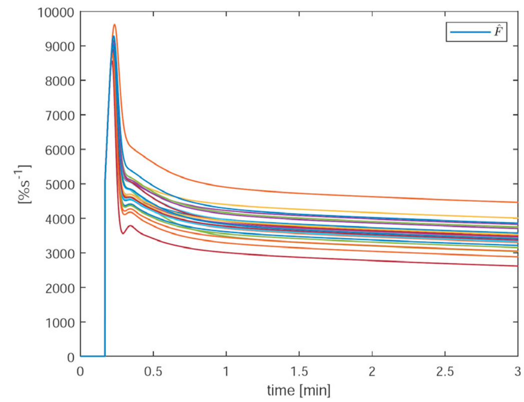


Fig. 5. $\hat{F}$ contains all system structural system-patient information and acts as an ingredient of the feed-forward action.

9a, 9b, 9c under the influence of disturbances like those shown in Fig. 3.

4.2 MIMO Example

The second example involves the 3-inputs and 3-outputs, where a fixed time delay equal to 10s is considered in the Poropofol-BIS interaction, over the 24 patients, during both induction and maintenance phases. The 3 ULM-iP controllers have been tuned using trial and error procedures and they regulate the BIS, RASS, and NMB by manipulating Propofol, Remifentanil, and Atracurium infusions. The performances of the 3 ULM-iP controllers are shown in Figs. 10a, 10b, 10c under the influence of disturbances like those shown in Fig. 3.

5. CONCLUSIONS

The paper employs the ultra-local model control approach for the automatic regulation of anesthesia. The method is quite straightforward and it ensures good performance in simulation both in the induction and maintenance phases, dealing with nonlinearities, noise effects, the time-varying BIS delay, intra- and inter-patient parameters variations, and unknown disturbances. Moreover, it exhibits interesting plug-and-play characteristics. Future developments will include an in-depth analysis of stability and tuning procedures for the proposed control approach.

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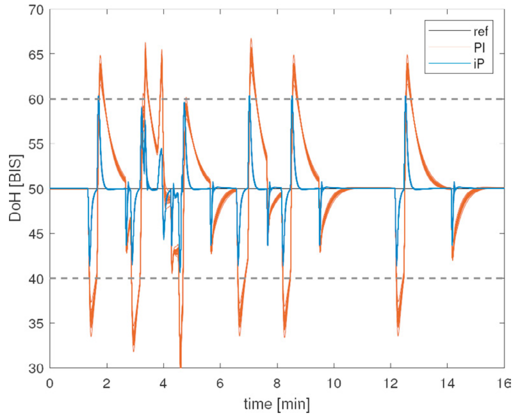
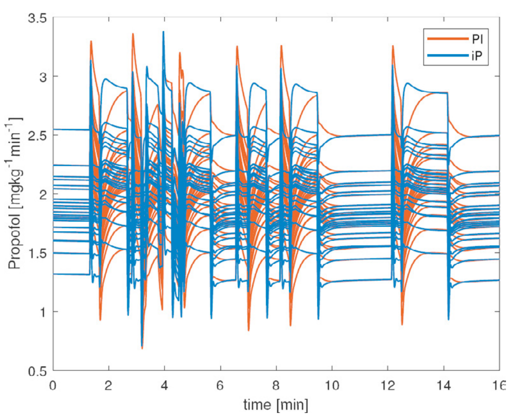
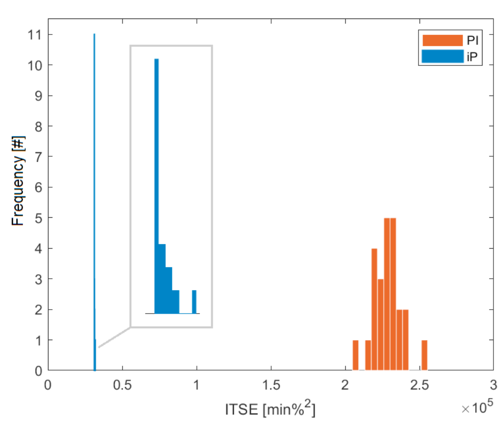


(a) BIS regulation.

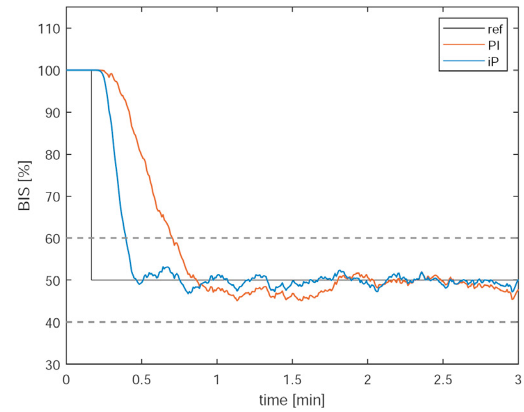


(b) Propofol infusion.

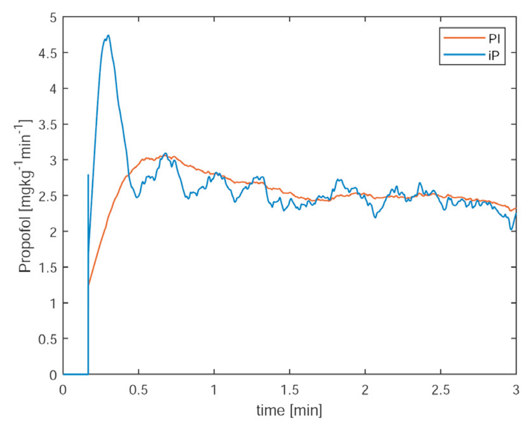


(c) Control performance: ITSE.

Fig. 6. BIS controlled by Propofol manipulation during maintenance phase under the influence of disturbances: ULM-iP (blue) vs PI (orange), 24 patients.



(a) BIS regulation. PI → ITSE = 8803min%^{2}; ULM-iP → ITSE = 1909min%^{2}.



(b) Propofol infusion.

Fig. 7. BIS control when an additive white Gaussian noise (zero mean and standard deviation equals 6.27) acts on the BIS output.

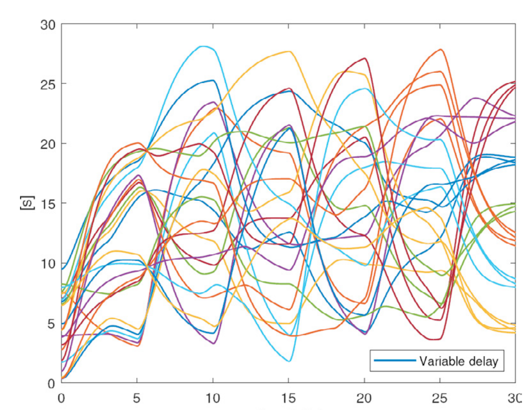


Fig. 8. Random time-varying delays over the 24 patients during induction and maintenance phases.

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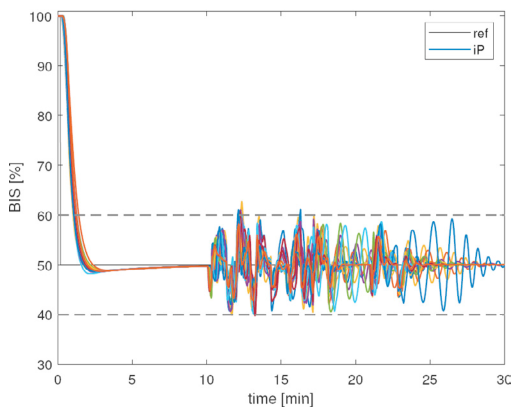
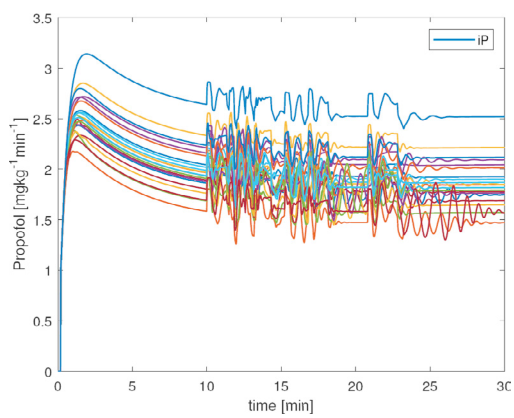
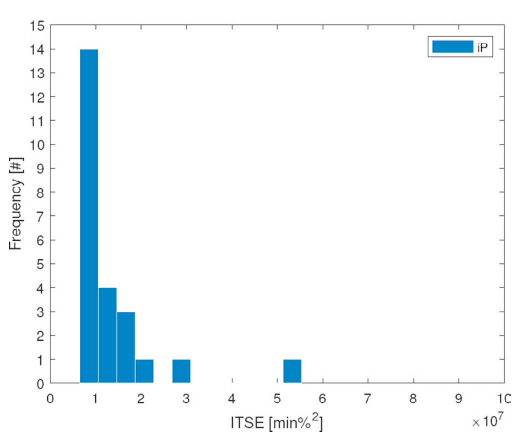


(a) BIS regulation.

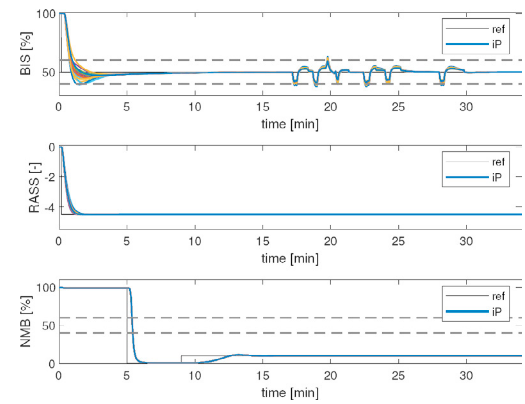


(b) Propofol infusion.

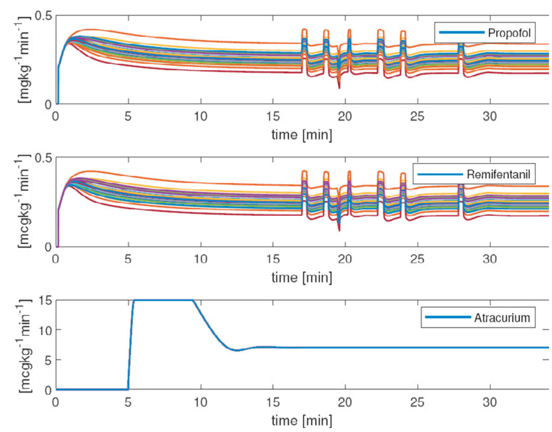


(c) Control performance: ITSE.

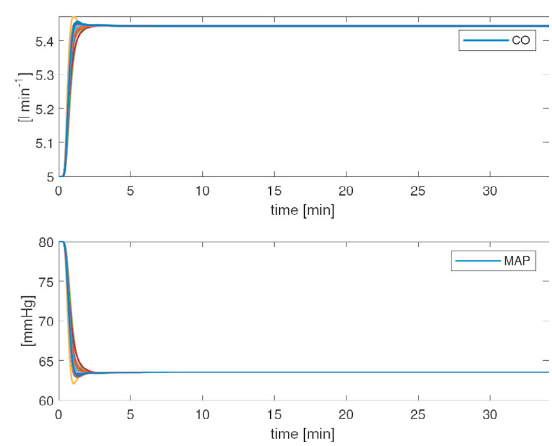
Fig. 9. BIS controlled by Propofol manipulation during induction and maintenance phases with time-varying delays under the influence of disturbances, 24 patients.



(a) BIS, RASS, and NMB regulations.



(b) Propofol, Remifentanil, and Atracurium infusions.



(c) Cardiac Output and Mean Aortic Pressure levels.

Fig. 10. MIMO control, BIS delay = 10s, under the influence of disturbances, 24 patients.

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