Preprints of the 9th IFAC Symposium on Biological and Medical Systems
The International Federation of Automatic Control
Berlin, Germany, Aug. 31 - Sept. 2, 2015

A gain-scheduled PID controller for propofol dosing in anesthesia

F. Padula [*] **C. Ionescu** [**] **N. Latronico** [***] **M. Paltenghi** [****]
A. Visioli [‡] **G. Vivacqua** [‡]

[*] *Department of Information Engineering, University of Brescia, Italy (e-mail: fabrizio.padula@unibs.it)*
[**] *Department of Electrical energy, Systems and Automation, Ghent University, Belgium (e-mail: ClaraMihaela.Ionescu@UGent.be)*
[***] *Department of Surgery, Radiology, and Public Health, University of Brescia, Italy (e-mail: nicola.latronico@unibs.it)*
[****] *Spedali Civili di Brescia, Italy (e-mail: maxpaltenghi@gmail.com)*
[†] *Department of Mechanical and Industrial Engineering, University of Brescia, Italy (e-mail: antonio.visioli@unibs.it)*
[‡] *Department of Mechanical and Industrial Engineering, University of Brescia, Italy (e-mail: g.vivacqua@studenti.unibs.it)*

Abstract: A gain-scheduled proportional-integral-derivative controller is proposed for the closed-loop dosing of propofol in anesthesia (with the bispectral index as a controlled variable). In particular, it is shown that a different tuning of the parameters should be used during the infusion and maintenance phases. Further, the role of the noise filter is investigated.

Keywords: Depth of hypnosis control, PID control, gain scheduling, genetic algorithms.

1. INTRODUCTION

The closed-loop control of drug dosing has been the subject of a significant research effort during the last years especially related to the surgery field, where an adequate anesthetic state has to be provided to the patient (Mortier et al., 1998; De Smet et al., 2007; Nogueira et al., 2014).
In principle, having a closed-loop automatic control of anesthesia might yield different benefits such as an increased safety, a reduced amount of drug used (so that the post operative recovery time of the patient is reduced) and a reduced workload for the anesthesiologist (who has in any case to supervise the overall surgery) (Bibian, 2006).
Actually, in general surgery, anesthesia can be classified into three functional components, that is, hypnosis, analgesia and immobility, and each component has its own drug to regulate it.
In this paper we focus on total intravenous anesthesia (TIVA) and, in particular, on the control of the depth of hypnosis (DoH) by means of propofol. The controlled variable is the bispectral index scale (BIS, Aspect Medical Systems, Norwood, USA), which measures the brain activity based on a bispectral analysis of the EEG of the patient (note that an alternative, similar measure is provided by the wavelet-based index (WAV_{CNS})).
During the surgery, three phases normally occur. At the beginning there is the induction phase when the patient is transitioned from consciousness to the required hypnotic state. From the control engineering viewpoint, this is a set-point following task that has to be performed as fast as possible without a significant overshoot which might result in a possibly dangerous hypotension (Lindholm et al., 2009). Then, the required hypnotic level has to be kept during the maintenance phase, where the task of the controller is to reject disturbances typically related to noxious stimuli. Finally, in the emergence phase the patient is recovered from the anesthesia by stopping the administration of the drugs.
It appears that the controller has to deal with different tasks. The process is usually modelled by using pharmacokinetic-pharmacodynamic models of the effect of propofol on the DoH. A linear time invariant model describes the relation between the propofol infusion rate and the plasma concentrations, while a nonlinear Hill function describes the relation between the plasma concentrations and the clinical effect. In this context, a large interpatient variability, that is, a large model uncertainty, has to be considered in the controller design.
In this context, different control strategies have been proposed in the literature. The first option is surely the well-known proportional-integral-derivative (PID) controller, which is the most adopted controller in industry owing to its capability to provide a good performance for a wide range of processes despite its simplicity. In fact, a PID controller has been proposed in (Yelneedi et al., 2009) but the tuning methodology has not been defined precisely. In (Dumont et al., 2009), the tuning procedure proposed in (Panagopoulos et al., 2002) is applied to a linearized model of the system (around the operating point) to achieve a satisfactory response to disturbances. Although a two-degree-of-freedom controller is used to handle the induction phase without overshoot, it has to be noted that the same PID parameters are used both in the induction and in the maintenance phases (that is, both for the set-point following and load disturbance rejection tasks). The same PID parameters (selected by a trial-and-error proce-

dure) for both tasks are also employed in (Hahna et al., 2012). A tuning procedure for the robust load integrated error minimization is used in (Soltesz et al., 2013) (the induction phase is controlled in open-loop or manually and the data collected in this phase are employed to identify the patient's model). Also in this case a linearized model is used for the tuning purpose. Finally, in (van Heusden et al., 2014) a robust design is proposed for the PID controller, again by exploiting a linearized model of the system.
Aiming at improving the PID controller performance, other methodologies have been proposed, such as model predictive control (Ionescu et al., 2008; Yelneedi et al., 2009), fractional control (Dumont et al., 2009) and μ-synthesis (Hahna et al., 2012).
Even if these methodologies are claimed to perform better than PID controllers, in this paper we propose a new design methodology for PID controllers, aiming at improving their performance and therefore to provide a benchmark for a fair comparison with other methodologies. In particular, differently from the approaches already proposed in the literature related to propofol dosing, the following issues are considered: (i) the PID parameters are selected separately for the induction and the maintenance phases, yielding a gain scheduled controller; (ii) the PID parameters are selected by considering a worst-case optimization on a set of patients in order to guarantee in any case that the approach is safe; (iii) the PID parameters are selected by considering explicitly the (static) nonlinearity of the process. Further, the role of the noise filter is investigated by analyzing the loss of performance that might occur in order to avoid an excessive actuator excitation. In order to pursue these objectives, a genetic algorithm is employed by considering a population of 12 patients (Ionescu et al., 2008). Even if the considered set can be seen as representative of a large population as very different kinds of patients are included, it cannot be claimed that it is exhaustive. However, the set is sufficient for the aim of the presented investigation, that is, showing that it is necessary to carefully consider the PID controller tuning before concluding that another controller provides a better performance.

2. PHARMACOKINETIC-PHARMACODYNAMIC MODEL

The overall effect of the propofol drug infused in the human body can be then modelled by considering the linear dynamics of its pharmacokinetics and pharmacodynamics in series with a static nonlinear function (Ionescu et al., 2008). Pharmacokinetics is usually described by means of a third-order transfer function $PK(s)$ with two zeros, where the parameters of the model can be obtained as suggested in (Schnider et al., 1998), where they depend on age, weight, height and sex of the patient. Pharmacodynamics is characterized by a first-order delay-free transfer function $PD(s)$ whose parameters depend on the metabolism of the drug and it is therefore independent from the patient (Schnider et al., 1998).
Then, the relation between plasma drug concentration C_e and clinical effect can be mathematically expressed by the means of a nonlinear sigmoid function, known also as Hill function, which models the bispectral index scale (BIS), a dimensionless parameter normalized between 0 and 100, indicating isoline EEG and fully awake patient respectively:

$$BIS(t) = E_0 - E_{max}\left(\frac{C_e(t)^\gamma}{C_e(t)^\gamma + C_{e_{50}}^\gamma}\right), \qquad (1)$$

where E_0 is the baseline value representing the initial infusion-free state of the patient, E_{max} is the maximum reachable effect achieved by the infusion, γ denotes the slope of the curve (*i.e.*, the receptiveness of the patient to the drug) and $C_{e_{50}}$ is the necessary concentration of the drug to reach the half maximal effect.
It is worth stressing that the Hill function is highly nonlinear. In fact, at the beginning of the infusion, the curve presents a *plateau*, where the presence of little quantities of the drug in the effect compartment does not affect the clinical effect until the drug concentration reaches a certain value. The final saturation expresses the impossibility to overcome the maximum achievable value E_{max} regardless of the amount of hypnotic infused.
In order to take into account the intrapatient variability, the dataset of patients presented in (Ionescu et al., 2008) has been employed. In addition to the set of 12 patients, a thirteenth individual has been considered as the average patient of the group, calculating for each available parameter its algebraic mean. The values of the model parameters for the considered population are presented in Table 1.

Id	Age	H [cm]	W [kg]	Gender	$C_{e_{50}}$	γ	E_0	E_{max}
1	40	163	54	F	6.33	2.24	98.8	94.10
2	36	163	50	F	6.76	4.29	98.6	86.00
3	28	164	52	F	8.44	4.10	91.2	80.70
4	50	163	83	F	6.44	2.18	95.9	102.00
5	28	164	60	M	4.93	2.46	94.7	85.30
6	43	163	59	F	12.00	2.42	90.2	147.00
7	37	187	75	M	8.02	2.10	92.0	104.00
8	38	174	80	F	6.56	4.12	95.5	76.40
9	41	170	70	F	6.15	6.89	89.2	63.80
10	37	167	58	F	13.70	1.65	83.1	151.00
11	42	179	78	M	4.82	1.85	91.8	77.90
12	34	172	58	F	4.95	1.84	96.2	90.80
13	38	169	65	F	7.42	3.00	93.1	96.58

Table 1. Characteristic variables for the considered set of patients (H: height, W: weight).

3. OPTIMAL TUNING OF PID CONTROLLERS

3.1 Control scheme

The employed control scheme is the standard feedback scheme shown in Figure 1 where the feedback controller is a PID controller whose transfer function is

$$C(s) = K_p\left(1 + \frac{1}{sT_i} + sT_d\right)\frac{1}{(T_f s + 1)^2} \qquad (2)$$

where K_p is the proportional gain, T_i is the integral time constant, T_d is the derivative time constant and T_f is the time constant of a second-order filter for the measurement noise (note that the use of a second-order filter is the most suitable solution as shown in (Segovia et al., 2014)). A standard anti-windup back calculation method (Soltesz et al., 2013) has also been implemented even if this issue is not critical for the provided tuning (see Section 3.2).
The control tasks are initially to track the set-point step signal r from the initial BIS value of the patient to a final value equal to 50 during the induction phase and then to reject the disturbances during the maintenance

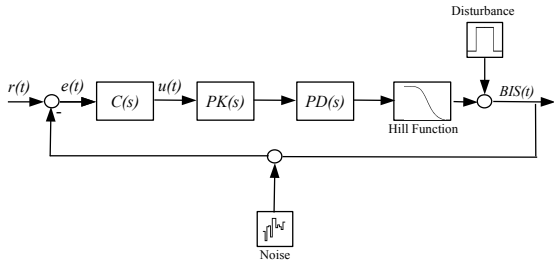

Fig. 1. The considered control scheme.

phase. Even if different disturbance patterns have been proposed in the literature for the controller evaluation (Struys et al., 2004; Dumont et al., 2009) here the one used in (Soltesz, 2013) has been considered as it allows an easy characterization of the control performance. It consists of a step signal of amplitude 10, acting directly on the process variable, followed by another step after 20 minutes of amplitude -10. Finally, measurement noise has been added to the feedback signal. This issue will be analyzed in Section 3.3.

3.2 Optimal PID tuning

The optimal PID parameters have been determined by employing a genetic algorithm (Mitchell, 1998) in order to minimize the integrated absolute error defined as

$$IAE = \int |e(t)|dt \tag{3}$$

in the worst case when all the patients are considered (see Table 1). Note that the set-point following and disturbance rejection have been considered separately. The IAE index has been selected as it considers a fast response without a significant overshoot at the same time. Further, in each case, two different limits for the control variable has been set, that is, 4.00 [mg/s] and 6.67 [mg/s]. The first saturation upper limit has been chosen by considering the usual clinical practice, while the second value has been chosen by taking into account the maximum rate of a standard medical pump and the concentration of propofol hypnotic drug.
Initially, the noise-free case has been considered. Results obtained by the genetic algorithm optimization are shown in Table 2 and in Figure 2 where the control variable is normalized with respect to the weight of the patient. It can be noticed that the tuning in case of disturbance rejection is more aggressive than the case of set-point following, as the proportional gain is bigger and the derivative time constant is smaller.

Case	Max rate [mg/s]	Worst-case IAE	Total infusion [mg]	K_p	T_i	T_d	T_f
Dist	4.00	1621.14	538.50	0.1055	889.3581	18.7711	0.8159
Dist	6.67	1659.34	538.43	0.0916	903.0916	14.9617	0.9092
SP	4.00	3374.55	239.92	0.0653	497.3168	36.2344	0.0476
SP	6.67	3278.65	241.65	0.0660	445.6125	39.9799	0.4310

Table 2. Optimal PID parameters for IAE minimization criteria (disturbance rejection and set-point following task). IAE and total infusion are calculated for the worst patient response among the set of patients.

3.3 Noise filter tuning

In the real application, the noise level of the BIS signal is very significant and this implies that a great attention

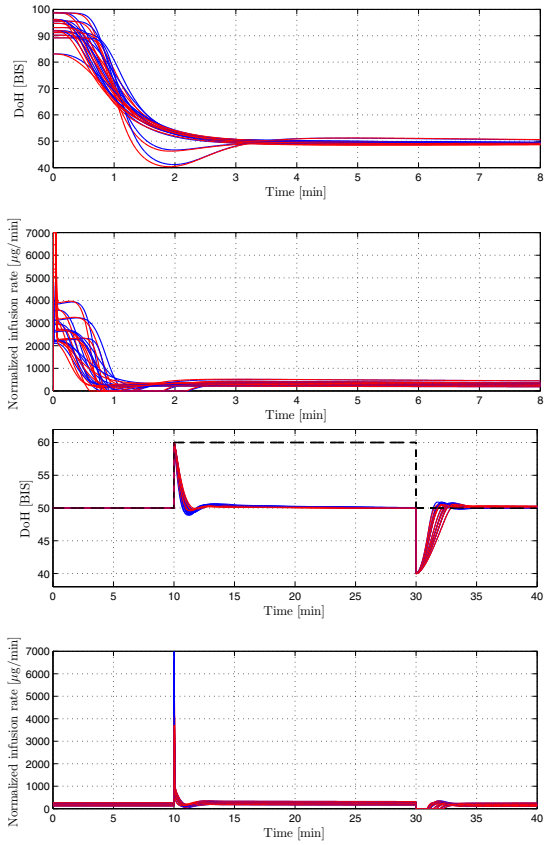

Fig. 2. Simulated patients response to propofol infusion. PID controller tuned for set-point following task (top), for disturbance rejection task (bottom). Maximum infusion rate of 4.00 [mg/s] (blue), or maximum infusion rate of 6.67 [mg/s] (red).

should be paid in tuning the (second-order) filter time constant. For this purpose, a simple method to tune the T_f parameter is then proposed.

- The set-point following and disturbance rejection tasks are considered as two separated case studies for the tuning procedure. Noise is introduced through an additive white Gaussian block with zero mean value and a standard deviation equal to $\sigma = 6.2721$; this latter value has been obtained from real BIS data. The PID parameters K_p, T_i, T_d have been set as they have been found from the noise-free optimization.
- The T_f time constant has been varied in a selected range, whose upper and lower limits are defined on the basis of the T_f values obtained in the corresponding tests without measurement noise.
- For each value of T_f, combined with the other PID parameters, the infusion response is calculated for all the patients in the considered set. If the minimum BIS value of a single patient response reaches a predefined undershoot threshold value, *i.e.*, falls below 25, the test is discarded and T_f is incremented.
- The calculated IAE indices are compared with the worst-case IAE obtained in the corresponding noise-free tests; the comparison is obtained through a performance decay ratio index defined as:

$$d_k = \frac{IAE_{noise,k} - IAE_{worst}}{IAE_{worst}}, \tag{4}$$

where $IAE_{noise,k}$ indicates the integrated absolute error value obtained with the selected T_f for the kth patient, and IAE_{worst} denotes the same index calculated for the worst response in the noise-free case and with the optimal output-filtered PID parameters determined by the genetic algorithm.

- For each iteration the filtering time constant T_f and the biggest decay among the patients are correlated; the correlation is not unique, considering that different T_f parameters can induce the same effect in percentage. In addition, not all the filter time constants lead to an evaluation because of the considered threshold undershoot condition, which limits the range of the possible selectable parameters.

The performance decay trends for the tuned time filtering T_f constants are presented in Figure 3. Black circles denote the filter time constants calculated for the noise-free cases, red and green stars indicate the lower and upper values of the filter parameters which induce respectively a 20% and 30% decay of the performance. Only the case with a maximum pump rate of 6.67 [mg/s] is shown for the sake of brevity, but results related to the other case are very similar.
This particular trend is obtained because:

- for low T_f values, filtering is not effective. Thus, measurement noise enters without almost any filtering in the controller, and it is amplified by the derivative action. Then, taking into account that noise is also zero mean, the main problem is the saturation block: indeed, the control variable normally operates closer to the lower saturation limit, hence noise is saturated asymmetrically. The process variable fluctuation induced by the noise presence can be easily managed by the positive actuator reaction, but when the variation forces the BIS index to decrease, the control variable cannot counteract, but only saturates to the zero lower saturation limit. High-frequency zero mean noise thus becomes high-frequency noise with non-zero mean. In other words, the additive input is seen as a bias the controller tries to compensate, changing the overall closed-loop dynamics, and perturbing the expected modelled behaviour. With a different dynamics the new IAE index calculated differs a lot from that obtained with the same parameters in the noise-free case, explaining the exponential decrease of the performance;
- for high T_f values, a significant dynamics is introduced in the overall system. Hence, the increasing difference between the output obtained in the noise-free simulation and the output in presence of measurement noise is due to the distortion the new dynamics induces;
- there exist particular T_f values which assure a fair noise filtering and at the same time preserve the decay of the performance. By setting the tuning parameter within these bounds, it is possible to realize a virtual tuning knob, that is, the tuning of the filter time constant can be done by imposing a tolerated decay for the infusion profile. Reasonable performance decay indices are between the 20% and 30%, which correspond to a balanced trade-off between the noise filtering and the optimal regulation. Furthermore, the concavity present in the curve offers the possibility to reach the same result with two different parameters. Obviously, the greatest between the two should be chosen in order to achieve a strongest noise reduction effect.

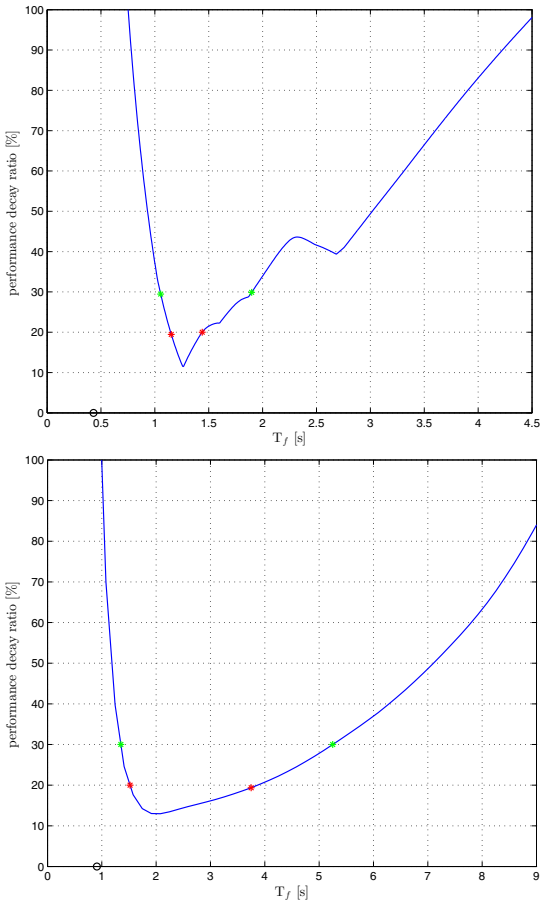

Fig. 3. Simulated performance decay ratio over the filtering time constant T_f for set-point following (top) and disturbance rejection (bottom). Maximum pump rate of 6.67 [mg/s]. Red stars: T_f parameters which lead to a decrease of 20% of IAE. Green stars: decrease of 30%. Black circle: noise-free optimal T_f parameter.

The results of the patients response in the presence of noise are shown in Figure 4. The blue lines represent the results of the noise-free simulations. The red and green lines denote the results in presence of the measurement noise where the filtering time constant T_f has been chosen to assure a maximum decay performance ratio respectively of 20% and 30%.
It can be noticed that the control variable resulting from the simulations is still noisy and it presents strong high-frequency variations due to the noise action. As previously mentioned, a trade-off between the noise reduction and the introduction of an additional dynamics exists. It is therefore interesting to evaluate also the performance that can be obtained by considering a PI controller without the derivative action.

3.4 Optimal PI tuning

The same procedure employed for PID controllers has been then applied to PI controllers (that is, by setting $T_d = 0$

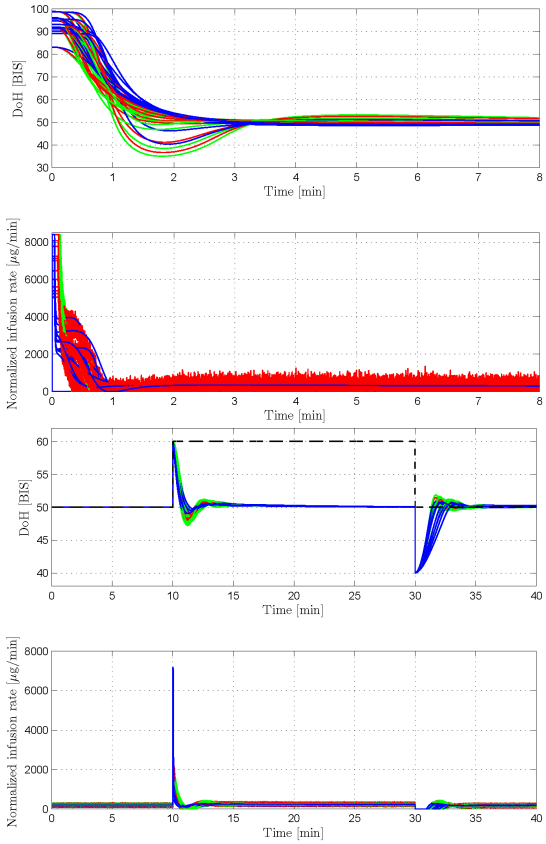

Fig. 4. Simulated patients response for set-point following (top) and disturbance rejection (bottom). Maximum pump rate of 6.67 [mg/s]. Responses in absence of noise (blue), and in presence of noise with a filtering action which leads to a maximum decay performance ratio of 20% (red) and 30% (green).

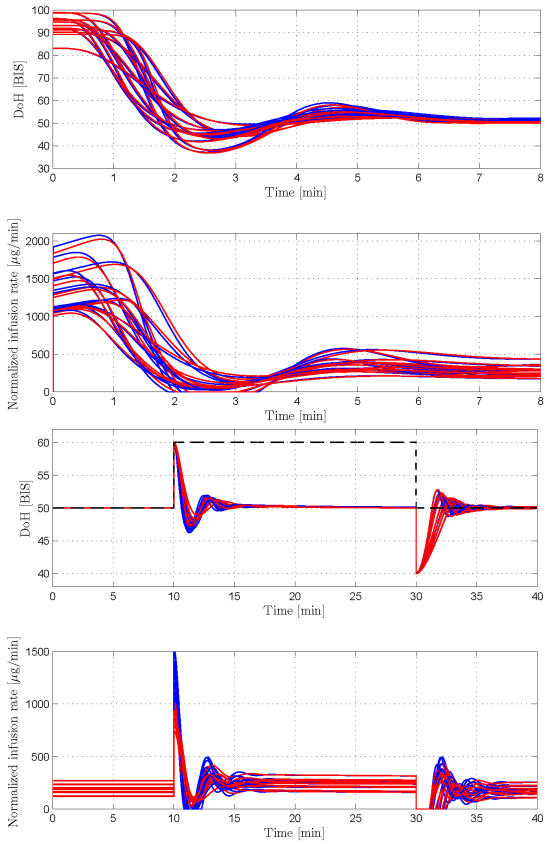

Fig. 5. Simulated patients response to propofol infusion. PI controller tuned for set-point following task (top), for disturbance rejection task (bottom). Maximum infusion rate of 4.00 [mg/s] (blue), or maximum infusion rate of 6.67 [mg/s] (red).

Case	Max rate [mg/s]	Worst-case IAE	Total infusion [mg]	K_p	T_i	T_f
Dist	4.00	1877.03	538.50	0.0795	906.4321	0.0107
Dist	6.67	1848.23	538.53	0.1088	1288.4393	0.0110
SP	4.00	5839.82	230.21	0.0329	482.6038	0.0161
SP	6.67	5756.36	232.21	0.0315	400.0012	0.0117

Table 3. Optimal PI parameters for IAE minimization criteria (disturbance rejection and set-point following task). IAE and total infusion are calculated for the worst patient response among the set of patients.

Task	Max rate [mg/s]	Worst-case IAE for dist	Worst-case IAE for SP	Decay [%]
Dist	4.00	1877	2210	17.78
Dist	6.67	1848	2110	14.19
SP	4.00	7580	5839	29.81
SP	6.67	8477	5756	47.28

Table 4. Integral absolute error decay calculated inverting the optimal parameters for a specific task.

in (2)). The optimal tuning resulting in the noise-free case are shown in Table 3 and in Figures 5. It appears the significant difference in the (optimal worst-case) tuning related to the set-point following and disturbance rejection tasks.
Regarding the tuning of T_f, considerations similar to the PID case can be done also in this case (results are not shown for the sake of brevity).

4. GAIN SCHEDULING APPROACH

The difference found during the optimal tuning for set-point following and disturbance rejection tasks suggests a gain scheduling technique. In particular, the PI(D) controller tuned for the set-point following task is employed only during the induction phase of anesthesia. Then, when the target is attained and the DoH is stabilized around the target for a predefined time interval, the controller parameters are switched to the disturbance rejection optimal ones (note that a bumpless switching has to be implemented).
In order to highlight the need of the gain-scheduled PI(D) controller, the responses of the patients when the tuning for the set-point tracking task is used for disturbance rejection and vice versa are shown in Figure 6 (a PI controller for the 6.67 [mg/s] case is considered as example). It is especially evident that, in the induction phase, the tuning devised for the load disturbance causes in some cases a long time interval where the control variable saturates and this yields an oscillatory behaviour and a possibly dangerous excessive overshoot.
The decay of performance calculated for the worst case among the patients set, inverting the optimal parameters of the specific tasks are shown in Table 4, confirming the effectiveness of the gain scheduling technique.

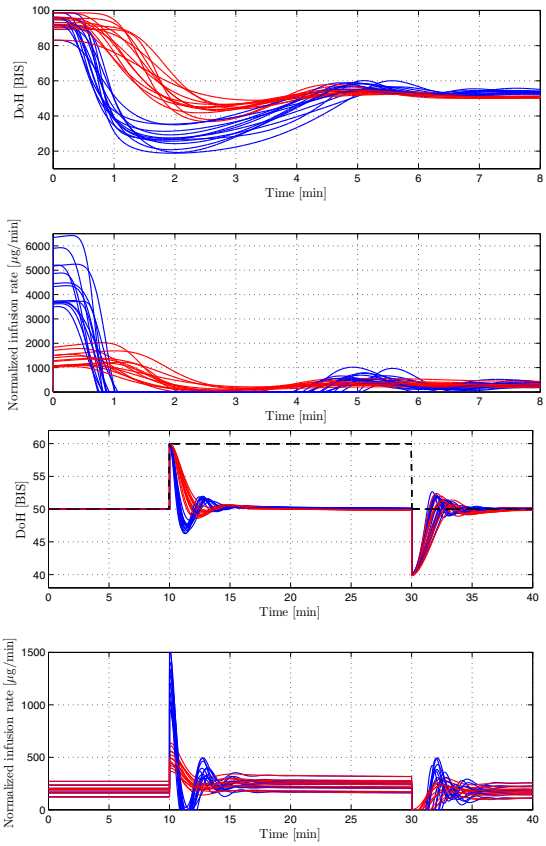

Fig. 6. Simulated patients response to propofol infusion for set-point following (top) and disturbance rejection (bottom) tasks. Maximum pump rate of 4.00 [mg/s]. Optimal set-point tuning (red), and optimal disturbance tuning (blue).

5. CONCLUSIONS

In this paper we have proposed a gain scheduling approach for the tuning of PID controllers for propofol dosing in anesthesia. In particular, we have shown that, if the PID parameters are optimally tuned by minimizing the worst-case integrated absolute error in the response of a given set of patients, it is worth considering the induction phase separately from the maintenance phase. Further, the noise filter time constant selection should be carefully done. It is worth noting that, even if the considered set of patients is obviously not exhaustive (although representative) of the overall population, it is sufficient to demonstrate the main concepts. It is therefore believed that advanced control strategies for anesthesia should be compared with optimally tuned PID controllers, where the control tasks are considered separately, the nonlinear model is explicitly taken into account, and the additional functionalities such as noise filter, anti-windup and so on are implemented.

REFERENCES

Bibian, S. (2006). *Automation in Clinical Anesthesia*. Ph.D. thesis, University of British Columbia (CA).

De Smet, T., Struys, M.M.R.F., Greenwald, S., Mortier, E.P., and Shafer, S.L. (2007). Estimation of optimal modeling weights for a bayesan-based closed-loop system for propofol administration using the bispectral index as a controlled variable: a simulation study. *Anesthesia and Analgesia*, 105(6), 1629–1638.

Dumont, G.A., Martinez, A., and Ansermino, J.M. (2009). Robust control of depth of anesthesia. *International Journal of Adaptive Control and Signal Processing*, 23, 435–454.

Hahna, J.O., Dumont, G.A., and Ansermino, J.M. (2012). Robust closed-loop control of hypnosis with propofol using $\mathrm{WAV}_C NS$ index as the controlled variable. *Biomedical Signal Processing and Control*, 7, 517–524.

Ionescu, C.M., Keyser, R.D., Torrico, B.C., Smet, T.D., Struys, M.M.R.F., and Normey-Rico, J.E. (2008). Robust predicitve control strategy applied for propofol dosing using BIS as a controlled variable during anesthesia. *IEEE Transactions on Biomedical Engineering*, 55(9), 2161–2170.

Lindholm, M.L., Traff, S., Granath, F., Greenwald, S.D., Ekbom, A., Lennmarken, C., and Sandin, R.H. (2009). Mortality within 2 years after surgery in relation to low intraoperative bispectral index values and preexisting malignant disease. *Anesthesia and Analgesia*, 108(2), 508–512.

Mitchell, M. (1998). *An Introduction to Genetic Algorithms*. MIT press.

Mortier, E., Struys, M., Smet, T.D., Versichelen, L., and Rolly, G. (1998). Closed-loop controlled administration of propofol using bispectral analysis. *Anaesthesia*, 53, 749–754.

Nogueira, F.N., Mendona, T., and Rocha, P. (2014). Controlling the depth of anesthesia by a novel positive control strategy. *Computer Methods and Programs on Biomedicine*, 114(3), e87–e97.

Panagopoulos, H., Astrom, K.J., and Hagglund, T. (2002). Design of PID controllers based on constrained optimisation. *IEE Proceedings – Control Theory and Applications*, 149, 32–40.

Schnider, T.W., Minto, C.F., Gambus, P.L., Andresen, C., Goodale, D.B., Shafer, S.L., and Youngs, E.J. (1998). The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology*, 88, 1170–1182.

Segovia, V.R., Hagglund, T., and Astrom, K.J. (2014). Measurement noise filtering for common PID tuning rules. *Control Engineering Practice*, 32, 43–63.

Soltesz, K. (2013). *On Automation in Anesthesia*. Ph.D. thesis, Lund University (S).

Soltesz, K., Hahna, J.O., Hagglund, T., Dumont, G.A., and Ansermino, J.M. (2013). Individualized closed-loop control of propofol anesthesia: a preliminary study. *Biomedical Signal Processing and Control*, 8, 500–508.

Struys, M.M.R.F., De Smet, T., Greenwald, S., Absalom, A.R., Binge, S., and Mortier, E.P. (2004). Performance evaluation of two published closed-loop control systems using bispectral index monitoring: a simulation study. *Anesthesiology*, 95(1), 6–17.

van Heusden, K., Dumont, G.A., Soltesz, K., Petersen, C.L., Umedaly, A., West, N., and Ansermino, J.M. (2014). Design and clinical evaluation of robust PID control of propofol anesthesia in children. *IEEE Transactions on Control Systems Technology*, 22(2), 491–501.

Yelneedi, S., Samavedham, L., and Rangaiah, G.P. (2009). Advanced control strategies for the regulation of hypnosys with propofol. *Industrial and Engineering Chemistry Research*, 48, 3880–3897.