Individualized PID Tuning for Maintenance of General Anesthesia with Propofol

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Abstract: In this paper we investigate a novel tuning methodology for a patient-individualized selection of the parameters of a proportional-integral-derivative (PID) controller that regulates the maintenance phase of general anesthesia. In particular, the knowledge of demographic data is exploited to determine the values of the parameters for each specific patient. The proposed approach is focused on the closed-loop administration of propofol by using the Bispectral Index Scale as controlled variable. Simulation results suggest that, with respect to a previously devised population-based PID tuning approach, the new methodology is more robust with respect to both intra-patient and inter-patient variability, at the cost of a slight decrement in the controller bandwidth.

Keywords: Depth of hypnosis control, PID control, individualized drug administration, personalized medicine.

1. INTRODUCTION

General anesthesia is a fundamental aspect in modern medicine as it allows invasive surgical procedures to be carried out without causing anxiety and pain to the patient. Thanks to the administration of specific hypnotic drugs, the activity of patient's central nervous system (CNS) is reduced to a level that induces unconsciousness and amnesia. Moreover, by administering analgesic drugs, the perception of painful stimuli is blocked and, in some cases, the administration of neuromuscular-blocking drugs is used to obtain paralysis of the skeletal muscles. In the practice of total intravenous anesthesia (TIVA), propofol is the most common hypnotic drug thanks to its fast redistribution and metabolism (Bibian et al., 2005) and relatively few side effects, if properly dosed (Tramer et al., 1997). Traditionally, the anesthesiologist decides the dosage of the initial bolus and the infusion rate during the maintenance phase depending on the physical characteristics of the patient, and by monitoring clinical indicators of the depth of hypnosis (DoH). DoH monitoring systems have been developed to provide the anesthesiologist with a quantitative measure of the clinical effect of hypnotic drugs on the CNS. The Bispectral Index Scale (BIS, Aspect Medical Systems, Norwood, USA) (Rampil, 1998) is one of the most widely employed measure of DoH in the clinical practice, and its effectiveness has been proven in numerous clinical studies (Struys et al., 1998). The BIS provides an estimate of the DoH through dimensionless number which varies from 0 (EEG silence) to 100 (patient fully awake). During anesthesia, this index should be kept in the range 40-60 for most kinds of surgeries (Rosow and Manberg, 2001). The availability of DoH indices has encouraged the development of closed-loop systems for automated drug delivery. Several control strategies have been proposed such as proportional-integral-derivative (PID) control (Dumont et al., 2009; Padula et al., 2017; Schiavo et al., 2021), event-based control (Merigo et al., 2017), model predictive control (Ionescu et al., 2008), fractional control (Dumont et al., 2009) and fuzzy control (Mendez et al., 2018). The relationship between propofol infusion and its clinical effect on DoH is traditionally modeled by a linear pharmacokinetic model, which describes the drug absorption and distribution, connected in series with a nonlinear pharmacodynamic model, which describes the relationship between the propofol blood concentration and its clinical effect. The nominal coefficients of the linear part depend on the patient's demographic parameters. The knowledge of these parameters helps to reduce model uncertainty. Conversely, the coefficients of the nonlinear part do not depend on any demographic parameter and show a great uncertainty that negatively affects the performance of closed-loop control systems. In order to deal with this issue, robust PID control strategies have been proposed, and

their feasibility has been demonstrated (Dumont et al., 2011; West et al., 2013; Padula et al., 2017; West et al., 2018). An alternative approach to handle uncertainty is the individualization of the controller design, which relies on using a specific controller for each individual, or for groups of patients who exhibit similar characteristics in response to drug administration. Large uncertainty limits the benefits of using complex control solution. Hence, reducing the effect of uncertainty is critical and provides a better alternative than implementing more complex control solutions, as highlighted in (van Heusden et al., 2018).

In this work we investigate a novel optimization-based PID tuning methodology that exploits the covariates of the Schnider's pharmacokinetic model for propofol (Schnider et al., 1998), i.e., the demographic data of the patient, to obtain a patient-individualized tuning. The proposed approach provides an optimal set of tuning parameters for each combination of covariates, thus providing an individualization of the controller dynamics based on the demographic data of the patient. The advantages of our approach in reducing the effects due to inter-patient and intra-patient variability are analyzed. In particular, we are interested in understanding whether a tuning of the PID controller that takes into account the covariates of the pharmacokinetic model can lead to some advantage despite the presence of the nonlinear pharmacodynamics. To this end, the results obtained in simulation with the new individualized tuning are compared with those obtained using an optimized population-based tuning (Padula et al., 2017).

2. MATERIALS AND METHODS

2.1 Patient model

As mentioned above, the tuning procedure presented hereafter is based on the simulation of patient response to propofol administration, hence an appropriate mathematical model is required. Although several models are available for propofol, in this work we have decided to rely on the so-called Schnider pharmacokinetic/pharmacodynamic (PK/PD) model (Schnider et al., 1998, 1999), since it has already been widely and successfully used in the design of closed-loop control systems (Schiavo et al., 2020). The dynamics of the patient is described by a fourth-order compartmental model which links the infusion rate of propofol to the effect-site concentration. The relationship between the effect-site concentration of propofol and the BIS is described by means of a nonlinear sigmoid, referred to as Hill function. The average parameters values presented in (Vanluchene et al., 2004) are used in this work. It is worth stressing that the parameters of the Hill function do not depend on the patient's demographics and are subjected to a large variability. Hence, the Hill function is a significant source of uncertainty in the model, and thus limits the performance achievable by closed-loop control systems.

2.2 Control system architecture

In this paper, we consider the control scheme shown in Figure 1. The feedback controller is a PID controller in

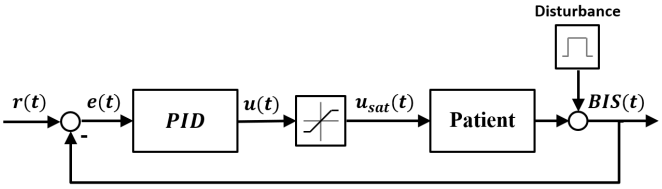

Fig. 1. Control scheme for the automatic administration of propofol during general anesthesia.

standard ideal form with filtered derivative term:

$$PID(s) = \frac{U(s)}{E(s)} = K_p \left(1 + \frac{1}{T_i s} + \frac{T_d s}{1 + \frac{T_d}{N} s} \right), \qquad (1)$$

where K_p is the proportional gain, T_i is the integral time constant and T_d is the derivative time constant. The derivative action is filtered with $N = 5$ in order to obtain a proper controller. Note that $E(s)$ is the Laplace transform of the error signal $e(t)$, which is calculated as the difference between the desired BIS value $r(t)$ and the actual BIS value $BIS(t)$, while $U(s)$ is the Laplace transform of the propofol infusion rate $u(t)$, which represents the control variable. The saturation block represents the lower and upper bounds of achievable infusion rates, which are 0 mg/s and 6.67 mg/s, respectively (Merigo et al., 2017). A conditional integration anti-windup strategy has been implemented (Visioli, 2006). The effect on DoH due to the surgical stimulation is modeled as an additive disturbance acting on the BIS signal. Here we use the model of disturbance proposed in (Soltesz, 2013), which consists of a step signal of amplitude 10 on the BIS, that simulates the arousal due to surgical stimulation, followed after 10 minutes by another step of amplitude -10, that brings the disturbance back to zero thus simulating the cessation of surgical stimulation. The control task consists in maintaining $BIS(t)$ as close as possible to $r(t)$ (which is set to 50) by rejecting disturbances while avoiding undershoots of the BIS below the value of 40 and raises of the BIS over the value of 60, since these situations could be harmful for patient's health.

2.3 Controller tuning

The proposed tuning methodology allows the PID parameters to be adjusted according to the patient's demographic data. In other words, the knowledge of patient's demographic data provides information about the system's dynamics which can be explicitly exploited in the tuning of the controller. Since the presence of nonlinearities prevents the use of analytical tuning methodologies, a heuristic method has been employed. In particular, a Particle Swarm Optimization (PSO) algorithm (Kennedy, 2011) has been used in order to find the set of values of K_p, T_i and T_d that minimizes the integral absolute error, defined as

$$IAE = \int_0^\infty |e(t)| dt. \qquad (2)$$

This performance index has been selected as, in general, it guarantees short settling times without large undershoots. Once the patient's age, weight, height and gender are known, the PK/PD model is constructed. As already mentioned, the average parameters values presented in

(Vanluchene et al., 2004) are used for the Hill function. This model is then used to run the PSO by simulating the response to the disturbance profile described in Section 2.2, eventually obtaining the set of optimal PID parameters that minimizes the IAE.

In order to verify how the PID parameters change according to patient demographics, a sample population has been generated, and for each individual, the optimal PID parameters have been calculated. For each gender, an individual of the population is characterized by the quadruple (A, H, W, G), where A stands for age, H for height W for weight and G for gender, and the entire population is the set $\{(A, H, W, G) \,|\, A = 20 + 10i; H = 150 + 5j; W = 50 + 5k; i, j, k \in \mathbb{N}_0; i \leq 7; j, k \leq 8; G \in \{F, M\}\}$ where F and M stand for female and male, respectively. The population covariates cover the following ranges, $age \in [20, 90]$ in steps of 10 years, $height \in [150, 190]$ cm in steps of 5 cm and $weight \in [50, 90]$ kg in steps of 5 kg, and for each combination of the above, there are both a female and a male individual. The optimal PID parameters obtained for each individual of the sample population are shown in Figure 2 where it is possible to observe that the optimal tuning parameters change significantly across the considered domain. To quantify the amount of change, we calculate the coefficient of variation (CV) for each parameter. For the given population/sample, CV is defined as (Brown, 1998):

$$CV = \frac{\sigma}{|\mu|} \cdot 100[\%], \tag{3}$$

where σ is the standard deviation and μ is the average. For males we have $CV_{K_p} = 22.40\%$, $CV_{T_i} = 15.44\%$ and $CV_{T_d} = 20.86\%$, while for females we have $CV_{K_p} = 25.28\%$, $CV_{T_i} = 15.28\%$ and $CV_{T_d} = 20.02\%$. The CVs are similar for both genders and the tuning parameter that shows the largest variability is the proportional gain K_p. Further, we notice that all the parameters show a monotonic behavior with respect to age (with the exception of T_d which shows a slight overlap for 80 and 90 years old individuals), see Figure 2. In particular, K_p and T_i decrease as age increases, while T_d increases as age increases. Note that K_p also shows a clear increasing trend with respect to height and weight. Finally, T_i and T_d show less noticeable trends with respect to weight and height, and they decrease slightly as the weight increases and remain almost unchanged as the height varies. The same considerations apply to both males and females.

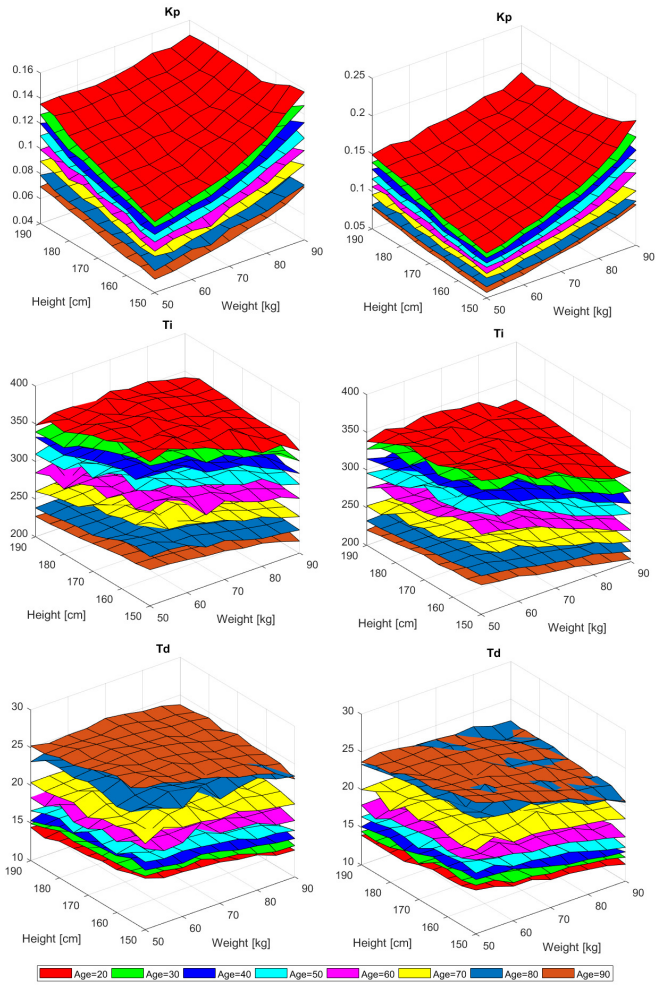

Fig. 2. Trends of the PID parameters for the sample population. The parameters for males are shown in the left column while the parameters for females are shown in the right column.

3. SIMULATION RESULTS

In this section the results obtained by testing the individualized tuning in simulation are reported. These results are compared with those obtained by employing the population-based PID tuning methodology proposed in (Padula et al., 2017) in order to understand the improvements that an individualized tuning brings with respect to a population-based approach. The tuning procedure proposed in (Padula et al., 2017) has been applied to the control structure described in Section 2.2 and the following population-based tuning parameters have been obtained: $K_p = 0.2013, T_i = 385.8701, T_d = 13.7577$. The simulation has been performed by simulating the maintenance phase of anesthesia in order to obtain a tuning suitable to reject disturbances, and therefore a fair comparison. The reference signal $r(t)$ is initially set equal to 50, the input and the states of the system are initialized as the equilibrium input and the corresponding equilibrium states such that $BIS(t) = 50$. Further, the integrator of the PID controller is preloaded to a value such that the control action in absence of tracking error equals the above-mentioned equilibrium input. Then, the disturbance profile described in Section 2.2 is applied. In order to evaluate the control performance, we use the following indices (Ionescu et al., 2008; Merigo et al., 2017):

- TT: observed time to target, which is the time taken to the controller to bring the BIS back in the interval 45-55 after the disturbance occurred. It is calculated separately for the positive and for the negative disturbance step, and it is referred to TTp and TTn, respectively.
- BIS-NADIRp: the lowest observed BIS value caused by the controller as a consequence of the disturbance rejection.
- BIS-NADIRn: the highest observed BIS value after the disturbance stops.

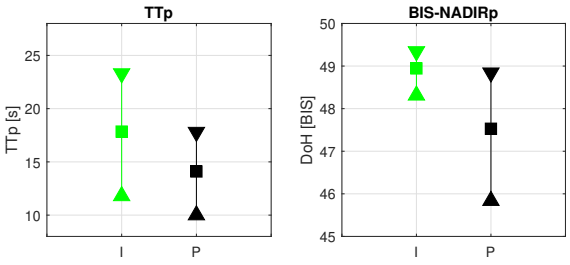

Fig. 3. Comparison of mean, minimum and maximum values of performance indices for the 13 patients of the test population obtained with the individualized tuning (I: green line) and with the population-based tuning (P: black line). ■ : mean value, ▲ : minimum value, ▼ : maximum value.

3.1 Test on a sample dataset

Initially the PID tunings have been tested on the dataset of patients presented in (Struys et al., 2004; Ionescu et al., 2008; Nascu et al., 2014; Padula et al., 2017). It represents a valid benchmark as it has been created on the basis of clinical studies in order to represent a wide range of population with significantly diverse responses to propofol administration. The dataset consists in 12 patients plus a thirteenth individual which is obtained by averaging the parameters of the other patients. Note that the population-based PID tuning used for the sake of comparison in this work has been obtained by minimizing the worst-case scenario over the above-mentioned dataset, while the individualized tuning is obtained by considering the values of the parameters of the Hill function described in Section 2.1. In order to better highlight the differences in the responses to the positive step disturbance obtained with the two different tunings, a comparison between the mean, minimum and maximum values of performance indices TTp and BIS-NADIRp is shown in Figure 3. Note that the TTp obtained with the individualized tuning is slightly longer than the one obtained with the population-based tuning. In particular, the individualized tuning shows a mean TTp of 17.8 s while the population based tuning shows a mean TTp of 14.1 s. Nevertheless, the TTp obtained with the individualized tuning remains clinically acceptable as the maximum value is 23.3 s. Furthermore, the higher TTp values obtained with the individualized tuning are counterbalanced by a reduction in the BIS-NADIRp. In particular, the population-based tuning shows a mean BIS-NADIRp value of 47.5 against the 48.9 obtained with the individualized tuning. This difference is even more evident if the minimum values are considered. Indeed, with the individualized tuning, a minimum BIS of 48.3 is reached against the minimum BIS of 45.8 obtained with the population-based tuning. The individualized tuning also shows a reduction in the variability of the BIS-NADIRp. Indeed, with the population-based tuning, a range of 3.0 is obtained among the 13 patients against a range of 1.0 obtained with the individualized tuning.

3.2 Test on a dataset subject to intra-patient variability

The behavior of the two different tuning approaches has been tested with respect to intra-patient variability, hence

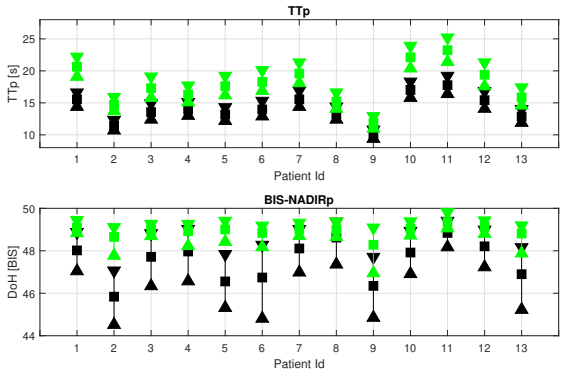

Fig. 4. Comparison of mean, minimum and maximum values of performance indices for each of the 13 patients of the test dataset subjected to intra-patient variability obtained with the individualized tuning (green line) and with the population-based tuning (black line). ■ : mean value, ▲ : minimum value, ▼ : maximum value.

against the variability within a group of patients with the same demographics. In order to simulate this variability, for each of the 13 patients of the considered dataset, a set of 500 perturbed models has been generated by a Monte Carlo method based on the statistical properties of the PK model given in (Schnider et al., 1998), and for each of these perturbed models the response to disturbance has been simulated. It is worth stressing that the individualized tuning procedure is still performed on the nominal model of the 13 patient, hence the tuning parameters are the same employed in Section 3.1, and the same set of parameters is employed for each one of the 500 perturbed models. The mean value, minimum value, maximum value and range for each of the thirteen patients of the dataset are shown in Figure 4. Even in the presence of intra-patient variability, the results obtained with the perturbed population shows similarity with those achieved on the dataset of the 13 nominal patients. In particular, the individualized tuning achieves higher values of the BIS-NADIRp, thus reducing the undershoot, at the cost of an increased value of the TTp with respect to the population-based tuning. As regards TTn and BIS-NADIRn, the same considerations made for the dataset of 13 nominal patients remain valid also for this more general case. Note that the individualized tuning achieves a reduction in the variability of BIS-NADIRp.

3.3 Test on a wide population

The behavior of the two different tuning approaches with respect to inter-patient variability has finally been assessed. A random population of 500 patients has been generated using a Monte Carlo method and the response to disturbance has been simulated for every individual. The patients have been generated by randomly selecting gender, by considering a uniform distribution of age between 20 and 90, of the Body Mass Index (BMI) between 18.5 kg/m^2 and 29.9 kg/m^2, and of the height between 165 cm and 190 cm for males and between 150 cm and 175 cm for females. For each patient, the weight has been calculated according to the selected height and BMI in

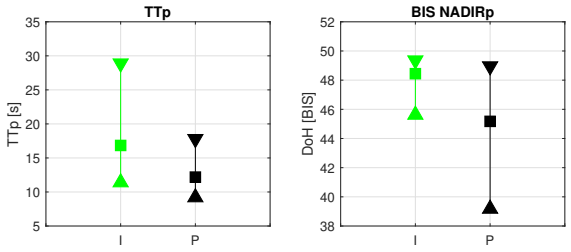

Fig. 5. Comparison of mean, minimum and maximum values of performance indices for the population of 500 patients used in order to simulate inter-patient variability obtained with the individualized tuning (I: green line) and with the population-based tuning (P: black line). ■ : mean value, ▲ : minimum value, ▼ : maximum value.

order to consider sensible height and weight combinations. The parameters of the Hill function have been generated by considering the statistical distribution given in (Vanluchene et al., 2004). The individualized tuning has been performed for each one of the 500 generated patients by considering the nominal model of the Hill function. As expected, even for a wider random population the same considerations made on the dataset of 13 patients apply. In particular, with the individualized tuning, we obtain an increase of the BIS-NADIRp index simultaneously reducing its variability, at the cost of an increased TTp index. Also in this case the TTn and BIS-NADIRn indices do not show significant differences between the two different tunings. The TTp and BIS-NADIRp indices obtained with both tuning methods are also shown in Figure 5 in order to facilitate the comparison. In particular, the minimum value of the BIS-NADIRp obtained with the population based tuning is 39.2 while a value of 45.6 is achieved with the individualized tuning. Conversely, the maximum value of the TTp index goes from 17.8 s with the population-based tuning to 28.9 s with the individualized tuning. However, with both tunings, the responses obtained meet the control specifications and are acceptable in clinical practice, even in the presence of inter-patient variability.

4. DISCUSSION

The proposed individualized tuning provided satisfactory control performance on the considered benchmark dataset. The individualized-tuning performed well in both the cases of intra-patient variability and inter-patient variability, always guaranteeing the fulfillment of the control specifications. In order to better understand the advantages and disadvantages that an individualized tuning can provide, the results obtained have been compared with those obtained with a population-based tuning. This comparison showed that the individualized tuning can effectively reduce the undershoot resulting from the rejection of a positive step disturbance, by reducing also its variability. This is consistently observed in all the tests carried out, and it is particularly evident especially in the case of inter-patient variability. Indeed, the minimum value of BIS-NADIRp reached with the population-based tuning is equal to 39.2, hence slightly below the lower BIS bound imposed by the control specification, while with the individualized tuning this value is equal to 45.6, hence well above the lower limit. Also the variability of BIS-NADIRp is significantly reduced, with the amplitude of the range of observed values dropping from 9.8 with the population based tuning to 3.7 with the individualized tuning. The reduction of the effect of variability achieved with the individualized tuning gives greater robustness with respect to BIS undershoot. However, this increase in robustness is paid for with a reduction in the controller bandwidth, which translates in an increase of the TTp index. As for the reduction of the undershoot, this is consistently observed in all tests, and it is especially evident in the case of inter-patient variability, with the maximum observed TTp values increasing from 17.8 s with the population-based tuning to 28.9 s with the individualized tuning. Also the variability in the TTp index increases with the individualized tuning, and the amplitude of the range of observed values increases from 8.6 s with the population-based tuning to 17.5 s with the individualized tuning. Hence, the population-based tuning is less sensitive to the effect of variability with respect to the time to target. It is worth stressing that, despite these different behaviors, both tunings guarantee the fulfillment of the control specifications, thus constituting two valid alternatives. The lower undershoot achieved with the individualized tuning makes it preferable in those situations and for those individuals where even slight overdosing should be avoided, for example, for patients with a high tendency to hypotension. On the other hand, the fastest disturbance rejection provided by the population-based tuning could be more suitable to reduce the risk of intraoperative awareness in situations where the patient is subject to strong surgical stimulation. In this work the individualization of the controller has been considered only for the maintenance phase of anesthesia since the induction phase of anesthesia is highly influenced by the presence of the Hill function, which introduces a strong nonlinear behavior. The individualization of the parameters relies on the knowledge of patient's demographic data that, as pointed out in Section 2.1, are not related to the parameters of the Hill function, but only affects the dynamics of the linear PK model. The Hill function shows strong nonlinearity for BIS values lower than 40 or greater than 60, while, in the range from 40 to 60, the Hill function behaves approximately like a constant gain. Hence, during the maintenance phase when the BIS remains mostly inside the range from 40 to 60, the dynamic behavior of the patient is less affected by the nonlinearity, and the proposed individualized tuning could provide more benefits.

5. CONCLUSIONS

In this work a novel PID tuning methodology which allows the controller parameters to be individualized on the basis of the patient's demographic data has been presented. The proposed approach allows the knowledge of all the patient's measurable covariates to be exploited and it is straightforwardly implementable in the clinical practice since covariates are easily measurable. The maintenance phase of anesthesia has been considered in order to minimize the effect of the nonlinearity introduced by the Hill function, which is particularly significant in the induction phase, since its parameters do not depend on patient's demographic data. The individualized tuning has been tested in simulation on a sample dataset and its

behavior with respect to intra-patient and inter-patient variability has been investigated. The controller has given satisfying results always guaranteeing the fulfillment of the control specifications. The results obtained in simulation with the individualized controller have been compared with those obtained with a PID controller tuned with a population-based methodology. The individualized controller has shown better robustness with respect to intra-patient and inter-patient variability, at the cost of a slight decrement of the bandwidth. This translates into an increase in the amount of time required to reject positive disturbances, which however remains within acceptable limits. Both tunings perform well in simulation and represent therefore viable alternatives for the tuning of PID controllers to be employed in the clinical practice.

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