

Fractional Order Control of the Combined Anaesthesia-Hemodynamic System: a Preliminary Study

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Abstract: Most surgical interventions involve sedating the patient with a cocktail of substances having anesthetic effects. The procedure is usually performed by a medical doctor that continuously monitors and readjusts drug dosage with respect to the patient's response. Current advances in automatic control and biomedical engineering offer the possibility to reassign the anesthetist's task to real-time, highly-performant monitoring and control algorithms, with the purpose of providing a risk-free anesthetic experience. The present study combines the well-known benefits of fractional calculus in biomedical applications with the intricate tasks revolving around automatic anesthesia. The proposed fractional order control algorithms are developed based on an open-source patient simulator that combines hemodynamics and anesthesia in a single customizable framework. Testing and validation of the proposed strategy is successfully performed on a group of 24 different patients in the presence of surgical stimulus. The ultimate result is that the hemodynamic characteristics are kept within accepted ranges, while a certain level of anesthesia is achieved.

Keywords: fractional calculus, hemodynamics control, anesthesia control, surgical stimulus, automatic control.

1. INTRODUCTION

According to (Gottschalk et.al. 2011) there are 230 million surgical procedures performed yearly under general anesthesia in the 56 member states of the World Health Organization (WHO). From the total number of surgeries, there is an anesthesia-associated death rate of 8.2/1 000 000 hospital discharges: 46.6% fatalities are caused by anesthetic drug overdose, 42.5% deaths are the result of side effects, whereas the other 10.9% is associated with various anesthesiological complications.

State of the art biomedical practice uses computer-based control of anesthesia for patient stabilization during surgical operations, intensive care units and rehabilitation periods (Magin et.al. 2018). Combining the benefits of automatic control with anesthetic practices outperform classical intravenous application techniques (Neckebroek et.al. 2013, Zaouter et.al. 2016). Automatic drug applications perform complex analysis of biomarkers in order to determine the optimal drug cocktails that provide patient stabilization, eliminating the need of an anesthesiologist to continuously monitor and readjust drug dosages (Joosten 2020, Zaouter 2020). Apart from the medical benefits brought by automatic anesthesia administration, there is also the managerial aspect of a limited number of anesthesiologists. In the current COVID-19 humanitarian crisis, lack of personnel often leads to specialized doctors caring simultaneously for an overwhelming number of patients, sometimes having to choose who to prioritize (McCartney 2020). Implementation

of automatic anesthetic control on a large scale solves both medical and managerial concerns of classical anesthesia.

An emerging topic in the field of system identification and automatic control is fractional calculus, a powerful tool that provides a generalization of differential operations to any arbitrary order. Going "in between" integer order differentiation operations offers a better representation of physical phenomena, with complex dynamics encapsulated in a reduced number of parameters. Fractional order calculus has been proven to be a better choice than integer order operators for both identification and control in a manifold of applications concerning different domains, including biomedical engineering (Birs et.al. 2019a, Birs et.al. 2019b, Monje et.al. 2010).

The present study focuses on the open-source patient simulator proposed by (Ionescu et.al. 2021). The control strategies should be developed such that the patient's hemodynamic variables are kept into acceptable intervals while reaching a desired level of anesthesia. The five controlled variables, Propofol, Remifentanyl, Atracurium, Dopamine (DP) and Sodium Nitroprusside (SNP) influence the hypnotic (BIS) and analgesic (RASS) states, neuromuscular blockade (NMB), cardiac output (CO) and mean arterial pressure (MAP). The benchmark can be customized with individual traits of every patient.

Previous related works such as (Birs et.al. 2019b, Ionescu et.al. 2010, Ionescu et.al. 2015) model and control individual parts of the hemodynamic or anesthesia process. Furthermore,

fractional order control strategies have been successfully used to control biomarkers such as MAP (Urooj and Singh 2019), depth of anesthesia (Sahoo et.al. 2020) or BIS regulation (Patel and Patel 2020).

The aim of the present study is to provide an efficient control strategy for anesthesia and hemodynamic processes taking into consideration the mingled interactions between the input and output variables. The choice of fractional order control is motivated by its superiority over integer order, classical, control strategies (Monje et.al. 2010) together with its proven benefits in biomedical engineering (Ghita et.al. 2020). A fractional order control system is designed for the combined anesthesia and hemodynamic system, considering a nominal patient model. Furthermore, the control strategy is validated on 24 different patients that respond differently to various drug cocktail inputs. The novelty of the manuscript consists in the first fractional order control strategy for the combined anesthesia and hemodynamic system.

The paper is structured as follows: Section 2 introduces some considerations on the combined hemodynamic and anesthesia system; Section 3 describes the frequency domain tuning methodology for the fractional order controllers; Sections 4 and 5 present the system identification and controller tuning; whereas Section 6 presents the closed system results obtained with the fractional order controllers. Finally, Section 7 concludes the paper.

2. HEMODYNAMIC AND ANAESTHESIA SYSTEM CONSIDERATIONS

The hemodynamic and anaesthesia models are developed based on the first patient in Table 1. The proposed control strategy is then tested and analyzed for the extra 23 patients included in this study. The characteristics of these 24 patients are indicated in Table 1.

An open loop analysis of the response of 24 patients is indicated in Fig. 1. The inputs used are step signals of Propofol: 0.5 mg/kg*min, Remifentanyl: 1.1 ug/kg*min and Atracurium: 6.5 ug/ml. The gain variations of the 24 patients can be clearly seen for BIS and RASS, whereas NMB responses are similar.

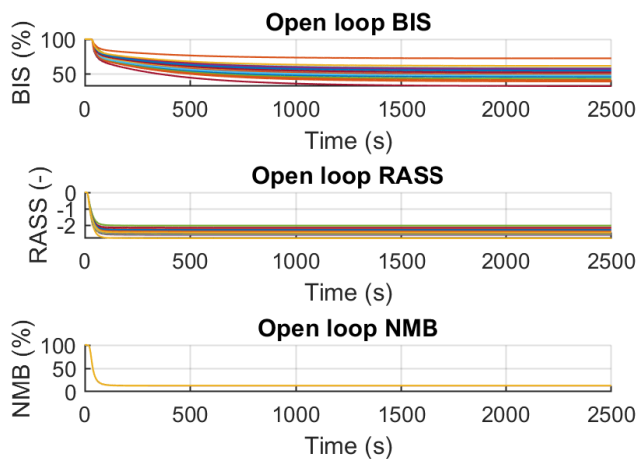


Figure 1. Open loop analysis of the response on the 24 patients

Propofol and Remifentanyl cause synergic effects on the BIS variable, while the Remifentanyl input lowers MAP and increases CO. Ultimately, increasing CO values leads to an increase of the clearance rates of Propofol, indirectly increasing BIS values. In addition, one should also consider the antagonistic effects between DP-SNP and CO-MAP. Direct cause effect models include the BIS variable (propofol drug rate to hypnotic state), RASS (Remifentanyl drug rate to analgesic state), NMB (Atracurium to neuromuscular blockade), CO (Dopamine to cardiac output) and MAP (Sodium Nitroprusside to mean arterial pressure). Based on this open loop analysis, a simple control strategy is designed based on FO-PIs controllers for each direct cause-effect models.

Table 1. Patient characteristics

Index	Age (years)	Height (cm)	Weight (kg)
1	74	164	88
2	67	161	69
3	75	176	101
4	69	173	97
5	45	171	64
6	57	182	80
7	74	155	55
8	71	172	78
9	65	176	77
10	72	192	73
11	69	168	84
12	60	190	92
13	61	177	81
14	54	173	86
15	71	172	83
16	53	186	114
17	72	162	167
18	61	182	93
19	70	167	77
20	69	158	81
21	69	158	81
22	60	165	85
23	70	173	69
24	56	186	99

3. TUNING METHODOLOGY FOR FO-PI CONTROLLERS

To control the overall hemodynamic and anesthesia system, fractional order PI (FO-PI) controllers are designed. Drug dynamics in Patient 1 are considered as nominal and the controllers are designed using a linear model.

The transfer function of the FO-PI controller is indicated below:

$$H_{FOC}(s) = k_p \left(1 + \frac{k_i}{s^\lambda} \right) \quad (1)$$

where k_p and k_i are the proportional and integral gains, while $\lambda \in (0,2)$ is the fractional. To tune the controller parameters standard FO-PI control strategies based on a frequency domain approach are used. The following three performance specifications are used (Monje et al., 2010), (Birs et al., 2019a):

1. A gain crossover frequency ω_c . This leads to the magnitude condition:

$$|H_{ol}(j\omega_c)| = 1 \quad (2)$$

with $H_{ol}(s)$ the open loop transfer function defined as: $H_{ol}(s)=P(s)H_{FOC}(s)$, where $P(s)$ is the process transfer function and $H_{FOC}(s)$ stands for the fractional order controller defined in (1).

2. A phase margin PM. This leads to the phase condition:

$$\angle H_{ol}(j\omega_c) = -\pi + PM \quad (3)$$

3. Iso-damping property (or robustness to gain variations). This is specified through:

$$\left. \frac{d(\angle H_{ol}(j\omega))}{d\omega} \right|_{\omega=\omega_c} = 0 \quad (4)$$

This last condition ensures that the overshoot of the closed loop system remains approximately constant in the case of gain variations. Robustness is one of the main advantage offered by fractional order control over integer order control strategies due to the additional isodamping constraint that can be imposed in the tuning procedure.

The three equations (2)-(4) can be rewritten as:

$$k_p \sqrt{1 + 2k_i \omega_c^{-\lambda} \cos \frac{\pi\lambda}{2} + k_i^2 \omega_c^{-2\lambda}} = \frac{1}{|P(j\omega_c)|} \quad (5)$$

$$\frac{k_i \omega_c^{-\lambda} \sin \frac{\pi\lambda}{2}}{1 + k_i \omega_c^{-\lambda} \cos \frac{\pi\lambda}{2}} = \tan(\pi - PM + \angle P(j\omega_c)) \quad (6)$$

$$\frac{\lambda k_i \omega_c^{-\lambda} \sin \frac{\pi\lambda}{2}}{1 + 2k_i \omega_c^{-\lambda} \cos \frac{\pi\lambda}{2} + k_i^2 \omega_c^{-2\lambda}} + \left. \frac{d\angle P(j\omega)}{d\omega} \right|_{\omega=\omega_c} = 0 \quad (7)$$

The FO-PI controller parameters are determined by solving the system of nonlinear equations (5)-(7). Optimization techniques or graphical methods can be used (Muresan et al., 2013), (Monje et al., 2010).

4. FO-PI CONTROLLER DESIGN FOR THE HEMODYNAMIC SYSTEM

The hemodynamic system is an important component in drug regulatory problems as it delivers drugs to the tissues and clears them from the body. The interaction between the drugs administered to maintain adequate cardiac output or MAP levels and those needed to achieve a certain depth of hypnosis also suggests that it is essential to design a control system that is able to minimize these interaction levels. A simplified multivariable system for the hemodynamic system has been used in this paper to capture the significant dynamics (Birs et.al. 2019b, Palerm and Buequette 2015, Ionescu et.al. 2021). The open loop tests on the benchmark system have shown that

the dynamics of this model varies corresponding to the patient changing sensitivity to drug rates – this translates into variations of gain in the model (De Keyser et al, 2015). The hemodynamic model has two inputs, i.e. dopamine and sodium nitroprusside, and two outputs, i.e. cardiac output and mean arterial pressure.

$$P(s) = \begin{pmatrix} \frac{5}{300s+1} e^{-60s} & \frac{12}{150s+1} e^{-50s} \\ \frac{3}{40s+1} e^{-60s} & -\frac{15}{40s+1} e^{-5s} \end{pmatrix} \quad (8)$$

A simple relative gain array analysis, as well as clinical experience, suggests that a diagonal pairing should be used in a decentralized control strategy: dopamine to control the cardiac output, while sodium nitroprusside is best used to keep MAP level in a safe range. For each loop, a FO-PI controller will be designed using the method described in Section 2. The performance specifications for controlling the CO level are: $PM=65^\circ$, $\omega_c=0.005$ rad/s, as well as the iso-damping property. For controlling the MAP output, a $PM=65^\circ$ is imposed, as well as $\omega_c=0.012$ rad/s and iso-damping. Solving in this case the system of nonlinear equations leads to the following FO-PI controllers:

$$H_{FOC-CO}(s) = 0.38 \left(1 + \frac{0.0012}{s^{1.2}} \right) \quad (9)$$

$$H_{FOC-MAP}(s) = 0.07 \left(1 + \frac{0.0034}{s^{1.27}} \right) \quad (10)$$

for cardiac output and MAP stabilization, respectively. The overshoot obtained in this case is 30%, whereas the settling time is 1268s (Birs et.al. 2019b). These results are similar to (Palerm and Bequette, 2015).

5. FO-PI CONTROLLER DESIGN FOR THE ANAESTHESIA SYSTEM

Tests on the benchmark system have indicated that a multivariable approach is needed to control the BIS and RASS values, as indicators of the depth of hypnosis and analgesia in patients. Little interaction is present in the NMB output due to variations of propofol or remifentanyl doses. Hence, the latter is controlled in a SISO fashion. Three FO-PI controllers are designed for each loop. Since RASS is affected by variations in remifentanyl, the FO-PI controller for this loop is firstly tuned. On the other hand, BIS levels are greatly changed by the synergistic effects of both propofol and remifentanyl doses. Once the RASS level is stabilized using the FO-PI controller, a fine tuning of the FO-PI controller for the BIS level is performed.

The performance specifications used to tune the FO-PI controller for the NMB output are: $PM=85^\circ$, $\omega_c=0.01$ rad/s, iso-damping property. Solving the system of equations in (5)-(7) leads to the following FO-PI controller that manipulates the atracurium dose:

$$H_{FOC-NMB}(s) = 0.08 \left(1 + \frac{0.0227}{s^{1.05}} \right) \quad (11)$$

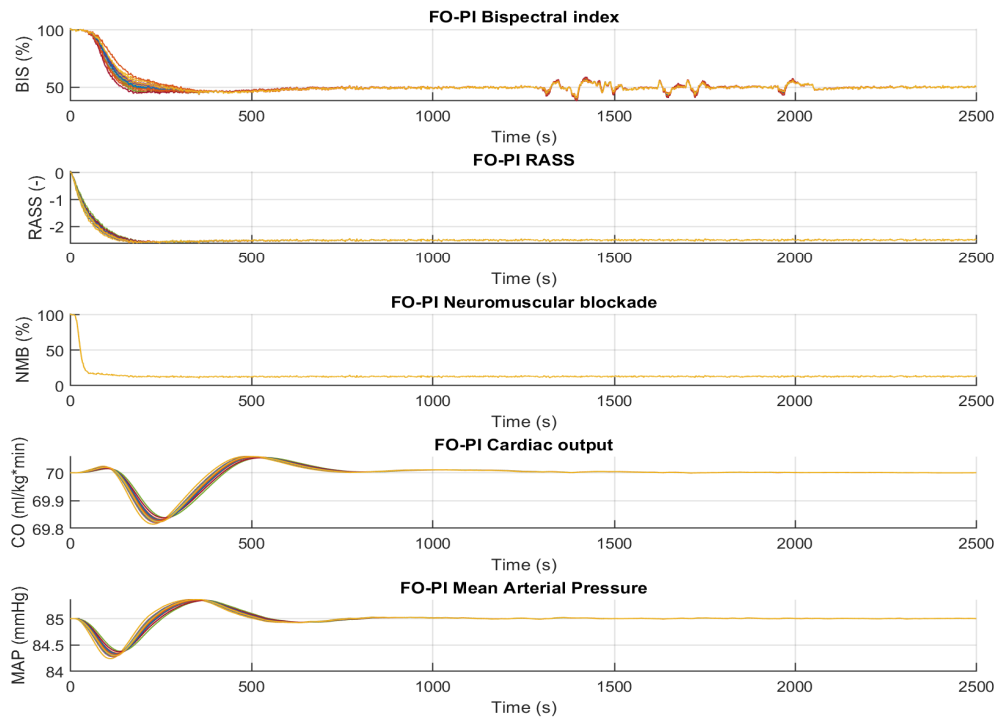


Figure 2. Closed loop system response with the FO-PI controllers on the 24 patients

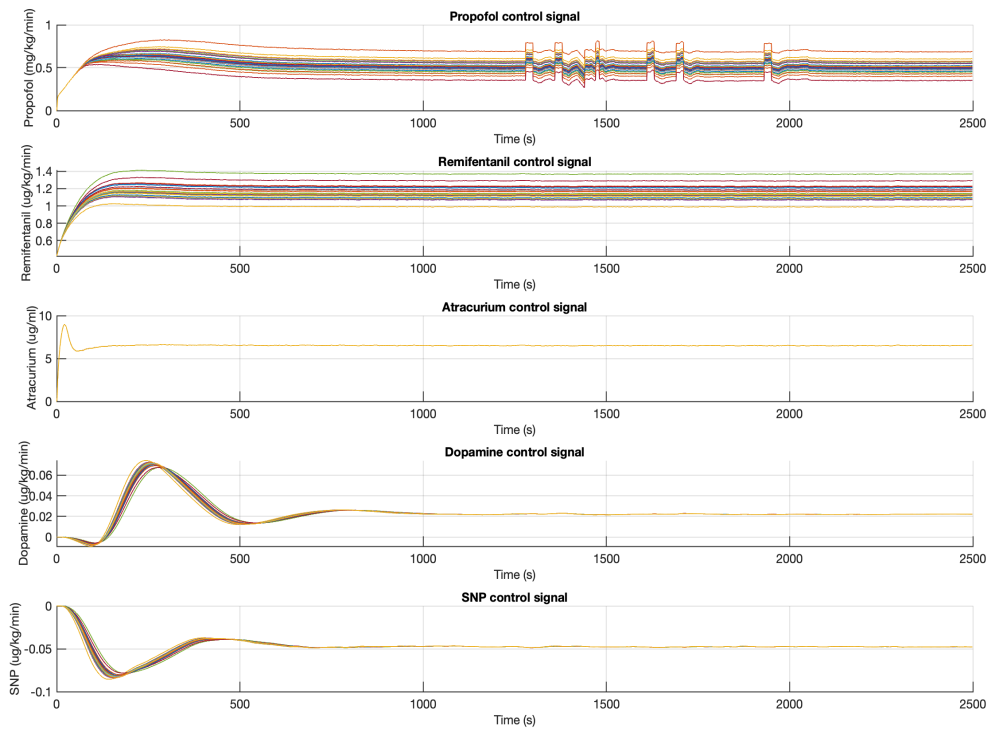


Figure 3. Computed control signals

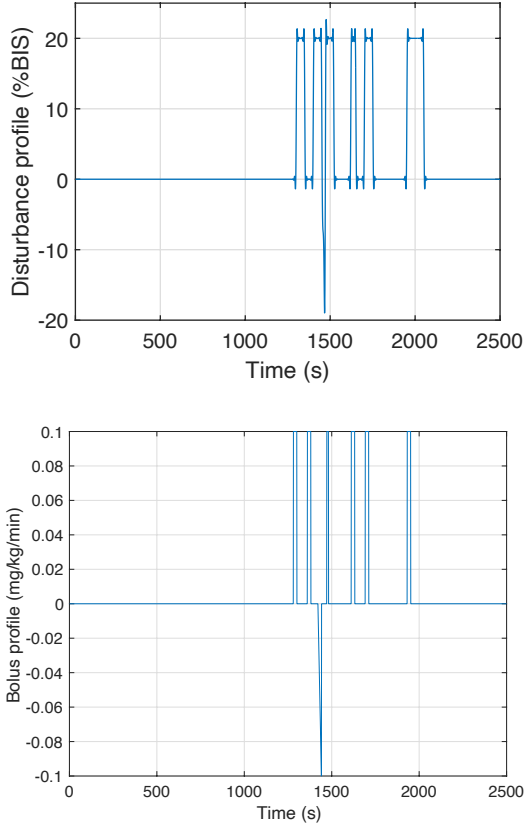


Figure 4. Disturbance profiles

Then, the RASS level is stabilised using a FO-PI controller tuned for a $PM=81^\circ$, $\omega_c=0.0185$ rad/s and iso-damping. The resulting FO-PI controller transfer function is given as:

$$H_{FOC-RASS}(s) = 0.17 \left(1 + \frac{0.0353}{s^{1.08}} \right) \quad (12)$$

Finally, a FO-PI controller is iteratively tuned in order to achieve a settling time of 4min (in the induction phase) with little undershoot, as well as good disturbance rejection and robustness. The final performance specifications that lead to the best closed loop results are $PM=85^\circ$, $\omega_c=0.012$ rad/s and iso-damping, while the transfer function of the FO-PI controller determined by solving the set of nonlinear equations (5)-(7) is:

$$H_{FOC-BIS}(s) = 0.0033 \left(1 + \frac{0.0273}{s^{1.054}} \right) \quad (13)$$

6. CLOSED LOOP SIMULATIONS

To test and validate the proposed fractional order control strategy, the nonlinear benchmark model in (Ionescu et.al. 2021) is used. For a more realistic simulation, white noise is added to each of the benchmark system's outputs. The closed loop system response of the 24 different patients from Table 1 is presented in Fig. 2 for the 5 output signals. Fig. 3 depicts the computed control signal with the FO-PI controllers. The following reference values are used to perform the simulation: BIS 50%, RASS -2.5 and NMB 13%. The values have been chosen with respect to realistic expectations of hemodynamic characteristics during anesthesia.

As can be seen in Fig. 2, the reference values are reached for all the output variables. The responses of the 24 different patients slightly differ, which was to be expected considering the open loop system responses shown in Fig.1. The induction phase performances vary between 120 and 260 seconds in terms of time-to-target (TT) the 55% BIS value and reach up to 5% in terms of undershooting for each individual. However, the outputs reach their reference values for all 24 patients avoiding the critical range of below 30% and above 70% leading to post-surgical complications and imminent awakening, respectively. The Cardiac Output Stabilization and Mean Arterial Pressure are successfully kept around 70 ml/kg*min and 85mmHg for the entire duration of the test.

Fig. 3 shows the control signals generated by the FO-PI controllers. The minimum and maximum allowed values with respect to real-life operating conditions limit Propofol between 0-5 mg/kg/min, Remifentanyl 0-2.5 mcg/kg/min, Dopamine 0-10 mcg/kg*min, SNP 0-10 mcg/kg*min and Atracurium in 0-15mcg/ml intervals. All control inputs computed for the hemodynamics and anesthesia process satisfy the previously mentioned min-max intervals. In the case of the hemodynamic system, an input value equal to 0 corresponds to a default dosage of the SNP and Dopamine drugs.

A surgical stimulus is introduced as a disturbance at time $t=1250s$ acting directly on BIS. Concurrently, mimicking the intervention of the anesthesiologist in order to compensate to some extent the expected disturbance profile an additional input signal, the bolus profile, is applied to the Propofol control value. Fig. 4 displays the disturbance for the duration of the entire simulation. The effects of the disturbance are displayed in Figs. 2 and 3 at time $t=1250s$ on the BIS and Propofol plots. As can be seen, the FO-PI controllers successfully reject the effects of the disturbances, keeping the signals in the desired BIS interval of 40 to 60%. The negative/positive values in Fig. 4 reflect either a decrease or an increase in the default doses.

7. CONCLUSION

The paper presents the tuning of various Fractional Order Proportional Integral controllers for controlling a combined system consisting of hemodynamics and general anesthesia. The hemodynamics system is modeled as a multi-input-multi-output system featuring first order transfer functions with time delay. The FOPI controllers are developed using a decentralized approach with the purpose of maintaining proper patients' hemodynamic values during anesthesia. The control strategy is successfully validated on an open-source patient simulator considering 24 different patients with varying physical characteristics. The fractional order controllers are successfully validated for reference tracking of the BIS, RASS and NMB markers in the presence of surgical stimulus and anesthetist in the loop.

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