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Robust Hemodynamic Control Under General Anesthesia Conditions ⋆

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Abstract: All drug regulatory paradigms are dependent on the hemodynamic system as it serves to distribute and clear the drug in/from the body. In this work, stabilization of hemodynamic variables within the context of maintaining general anesthesia conditions is presented. Several methods for robust control are employed, all based on the emerging fractional order control algorithm with inherent robustness to gain and phase margin variations. These are important due to the inter- and intra- patient variability at hand. The results indicate the great suitability of fractional order control as a substantially robust algorithm which can be used in combination with regulatory schemes for better closed loop performance. The challenges of the hemodynamic system under analysis here is the high coupling (multivariable system) with delay-dominant dynamics. Additionally, disturbance from the anesthesia-regulatory system and realistic surgical stimulation profiles are incorporated to complete the analysis. The results support the claims.

Keywords: hemodynamic regulation, anesthesia regulation, delay dominant dynamics, multivariable control, fractional order control

1. INTRODUCTION

Regulatory loops for drug dosing problems create increased awareness in the medical and engineering community, as the information technology tools penetrate increasingly into these areas (Beck, 2015). Applications thereof vary from diabetes (Kovacs, 2017), cancer (Drexler et al., 2011), anaesthesia (Copot and Ionescu, 2014), immunodefficiency (Popovic et al., 2015) and hormonal treatment (Churilov et al., 2009), to mention a few. There is sufficient evidence to indicate that closed loop control of drug dosing systems for anaesthesia perform better than manual control (Neckebroek et al., 2013). These systems rely on the availability of a model which often is defined as compartmental models with additional nonlinear functions to account for pharmacokinetics (PK) and pharmacodynamics (PD), respectively (Ionescu et al., 2008, 2015; Padula et al., 2016, 2017; Mendonca et al., 2009). Drug intake, uptake and clearance have been characterized using either compartmental models, either input-output filters by means of linear transfer functions (Schuttler and Schwilden, 2008). Standardly, compartmental models for drug kinetics are available in the literature from population data and are based on Gaussian normalized distributions. Additional dynamic response in drug effect is added as a PD additional compartment, usually nonlinear. The PK-PD models then combined to deliver the response to a drug input administered either oral or intravenous, of an average patient. However, these average patient models are no longer valid in the framework of personalized medicine, (again, irrespective of the medical application).

The complete anesthesia regulatory paradigm is however much more complex that anything literature addresses from control engineering point of view hitherto (Bibian et al., 2005). The computer based drug dosing optimisation is always limited in the information it receives from the system (i.e. vital signals from the patient). In general anaesthesia, the anaesthesiologist provides a cocktail of optimal dosages of various drugs to induce and maintain this complex physiological state in the patient, while avoiding under- and over-dosing, and coping with great patient variability (Keyser et al., 2015; Copot and Ionescu, 2014). Three components define the general anesthesia state of patient: hypnosis (lack of awareness, lack of memory), analgesia (lack of pain) and neuromuscular blockade (lack of movement). The literature both clinical and biomedical engineering, both with roots in systems and control theory, have proposed numerous schemes to induce and maintain hypnosis and neuromuscular blockade (Ionescu et al., 2008, 2015; Padula

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et al., 2016, 2017; Mendonca et al., 2009) and these two aspects of anesthesia are now mature for integration in a single environment. Hypnotic and opioid (analgesic medication) side-effects mark changes in other biosignals as heart rate, respiratory rate, mean arterial pressure gas in- and ex-piratory percentages, body temperature, etc. Hence, methods from artificial intelligence and data mining domains have proven to be useful tools, e.g. fuzzy logic (Shieh et al., 2007, 2006), neural networks (Haddad et al., 2007) etc. As such, pain is a complex process, involving a manifold of chemical, physical and electrical sub-processes all sequenced in a systemic context.

Management of hemodynamic state (such as cardiac output, mean arterial pressure) is of key importance in both the operating room and the intensive care unit. Monitoring of high risk patients is a challenging task for the anesthesiologists. It has been shown that cardiac output optimization improves the outcome of high risk patients from the point of view of hospitality stay, mortality rate, post-operative complications, etc. (Donati et al., 2007; Lobo et al., 2006; Pearse et al., 2005). Intraoperative mean arterial pressure influences clinical outcomes (Davis et al., 2012; Wang et al., 2015; Togashi et al., 2015).

In this paper a robust control strategy for hemodynamic part under the conditions of general anesthesia is proposed. The paper is structured as follows: In Section II the materials and methods employed to investigate the complex issue of controlling the hemodynamic variables within the context of general anesthesia is presented. In Section III the the obtained results are discussed followed by Section IV where the conclusion of the study as well as the future work are addressed.

2. MATERIALS AND METHODS

2.1 System description

The pharmacokinetic part of the hypnosis model is a transfer function model of the form

$$P(s) = \frac{K(s+z_1)(s+z_2)}{(s+p_1)(s+p_2)(s+p_3)(s+p_4)} \tag{1}$$

with parameters $z_1 = -10; z_2 = -15; p_1 = -1; p_2 = -0.8; p_3 = -0.02; p_4 = -0.5$ and $K = -0.005$ adapted from (Soltesz et al., 2013; Bibian et al., 2005). The input of this model is then Propofol (mg/kg*min) and the output is effect site concentration CeP (mg/ml). The PD part of the hypnosis model is a nonlinear Hill curve in the form

$$Effect = \frac{CeP^{\gamma_P}}{CeP^{\gamma_P} + C50P^{\gamma_P}} \tag{2}$$

where CeP is the output of the PK model from (1), $C50P$ is the concentration at half-effect and γ_P denotes the drug resistance/sensitivity of the patient. For this simulator, the values $C50P = 2.2$ and $\gamma_P = 2$ have been used, as from clinical data reported in (Bibian et al., 2005; Yang et al., 2015). A simplified form of the Hill curve can be used if adaptation online (during drug titration in presence of surgical stimulus) is necessary, as suggested in (Ionescu, 2018).

There is evidence to support the claim that sedative and hpnotic drugs affects negatively mean arterial pressure (MAP) and a model has been approximated from (Standing et al., 2009):

$$MAPfromP = \frac{-1}{0.81 * 15s + 0.81} \tag{3}$$

followed by a pharmacodynamic model with $\gamma_{PMAP} = 4.5$ and $C50_{PMAP} = 17$.

The hemodynamic model has been taken from (**?**) and has two inputs: Dopamine (DPM) and Sodium Nitroprusside (SNP), and two outputs: Cardiac Output and MAP.

This model has been successfully controlled with fractional order control as it has inherent robustness to delay variability (which is the major uncertainty here) and reported in (Copot et al., 2018).

2.2 Tuning of FO controllers for the hemodynamic system

Consider a simplified multivariable system, as the model of the hemodynamic system to be stabilized during surgery and general anesthesia procedures. This is an approximated model capturing the essential dynamics as reported in specialised literature (Palerm and Bequette, 2015). The patient variability requires automatic tuning of the controller parameters, but also robustness for the patient changing sensitivity to drug rates – this translates into variations of gain in the model (Keyser et al., 2015). This model has two inputs, i.e. dopamine and sodium nitroprusside, and two outputs, i.e. cardiac output and mean arterial pressure:

$$P(s) = \begin{pmatrix} \frac{5}{300+1}e^{-60s} & \frac{12}{150s+1}e^{-50s} \\ \frac{3}{40+1}e^{-60s} & -\frac{15}{40+1}e^{-5s} \end{pmatrix} \tag{4}$$

This process will further be used as to mimic the system to which the proposed methodology will be applied to obtain necessary information for automatic tuning of controller gains. The methodology is explained in the next section.

Four fractional order control strategies suitable for multivariable time delay systems (as the hemodynamic model) have been applied to the process indicated in (4).

1. Design of fractional order PI controllers for each input-output pair, based on a decentralized approach The method used in this approach attempts to determine the parameters of the fractional order PI (FO-PI) controller described by the following transfer function:

$$C_{PI}(s) = k_p\left(1 + \frac{k_i}{s^\alpha}\right) \tag{5}$$

where k_p and k_i are the proportional and integral gains and λ is the fractional order, with $\lambda_{min} < \lambda < 2$, with the minimum value for the fractional order computed as indicated in (Muresan et al., 2019). The FO-PI controllers are tuned individually for each of the two input-output pairs in (4), based on a set of three performance criteria: phase margin, gain crossover frequency and iso-damping (Muresan et al., 2013; Monje et al., 2010). The three performance specifications are described as follows:

$$|H_{OL}(j\omega_c)| = 1 \tag{6}$$

$$\angle H_{OL}(j\omega_c)| = -\pi + PM \tag{7}$$

$$\frac{\angle H_{OL}(j\omega_c)}{d\omega_c} = 0 \tag{8}$$

where $|\ .\ |$ stands for modulus of a transfer function, while $\angle$ represents its phase and $H_{OL}(s) = C_{PI}(s)H_P(s)$ is the open loop transfer function, with HP(s) – the process to be controlled. The three parameters of the controller in (5) can be easily determined using optimization algorithms or graphical methods (Muresan et al., 2013; Monje et al., 2010).

A simple relative gain array analysis suggests that diagonal pairing should be used in a decentralised control strategy. Thus, two FO-PI controllers will be designed to control the cardiac output and the mean arterial pressure by manipulating the dopamine level and sodium nitroprusside, respectively. For both loops, a phase margin $PM = 65^o$ is imposed, as well as the iso-damping property. For the first loop, the gain crossover frequency is imposed to be $\omega_{c1} = 0.005\ rad/s$, while for the second loop, $\omega_{c2} = 0.012\ rad/s$. These frequencies are selected in order to reduce the settling time of the hemodynamic system. The tuning procedure yields the following parameters: $k_{p1} = 0.3481$, $k_{i1} = 0.0012$ and $\lambda_1 = 1.2$ for the first controller and $k_{p2} = 0.07$, $k_{i2} = 0.0034$ and $\lambda_2 = 1.27$, for the second one (Birs et al., 2019a,b).

2. Design of fractional order PI controllers, combined with a decoupling strategy

A steady state decoupling strategy is attempted, using the inverse of the steady state process transfer function matrix in (4):

$$P(0)^{-1} = \begin{pmatrix} 0.1351 & 0.1081 \\ 0.0270 & -0.0450 \end{pmatrix} \tag{9}$$

The decoupled process transfer function matrix is then obtained as:

$$P_D(s) = P(s) \times P(0)^{-1} \tag{10}$$

in which all elements are weighted sums of the original transfer functions in (4) . Due to the static decoupling, in steady state the transfer function matrix $P_D(s = 0)$ will be equal to the unit matrix. Thus, the non-diagonal terms in the $P_D(s)$ decoupled process transfer function matrix would be zero in steady state conditions; consequently, only the diagonal terms in (10) will be further used in the design of the controller, with each diagonal term corresponding to a specific process output. First, the elements on the diagonal are approximated to simple transfer functions (Muresan et al., 2015, 2016a) as:

$$D_1(s) = \frac{1}{253s+1}e^{-51s}; D_2(S) = \frac{1}{42s+1}e^{-51s} \tag{11}$$

Then, two FO-PI controllers are designed for the these diagonal elements in (11). The same tuning procedure as mentioned above is used, based on specifying a certain phase margin, gain crossover frequency and iso-damping. For both transfer functions in (11), a phase margin $PM = 65^o$ is imposed, as well as the iso-damping property. For the first loop, the gain crossover frequency is imposed to be $\omega_{c1} = 0.008\ rad/s$, while for the second loop, $\omega_{c2} = 0.015\ rad/s$. The decoupling allows for more strict performance specifications, with increased gain crossover frequencies values. The tuning procedure yields the following parameters: $k_{p1} = 2.76$, $k_{i1} = 1825.08$ and $\lambda_1 = 1.16$ for the first controller and $k_{p2} = 1.09$, $k_{i2} = 318.73$ and $\lambda_2 = 1.28$, for the second one.

3. Design of fractional order PI controllers, in a Smith Predictor control structure, with a decoupling compensator

The same steady state decoupling strategy is used here as mentioned above, but the Smith Predictor structure is used to compensate for the time delays (Birs et al., 2019b). The corresponding FO-PI controllers are designed for the decoupled delay-free process, based on the same tuning procedure as previously: a certain phase margin, gain crossover frequency and iso-damping are imposed as design constraints. The delay free decoupled input-output pairs for which the two controllers are designed are similar to (11):

$$D_{1SP}(s) = \frac{1}{253s+1}; D_{2SP}(S) = \frac{1}{42s+1} \tag{12}$$

For both transfer functions in (12), a phase margin $PM = 65^o$ is imposed, as well as the iso-damping property. For the first loop, the gain crossover frequency is imposed to be $\omega_{c1} = 0.01\ rad/s$, while for the second loop, $\omega_{c2} = 0.1\ rad/s$. The decoupling and Smith Predictor structure allows for even more strict performance specifications, with increased gain crossover frequencies values compared to the previous cases. The tuning procedure yields the following parameters: $k_{p1} = 1.45$, $k_{i1} = 39.07$ and $\lambda_1 = 0.87$ for the first controller and $k_{p2} = 2.15$, $k_{i2} = 3.89$ and $\lambda_2 = 0.72$, for the second one.

4. Design of fractional order controllers, in a fractional order IMC methodology

In this approach, first the steady state decoupling is performed. The Smith Predictor structure is used and therefore the fractional order controllers are designed for the transfer functions in (12), represented in a generalized way as:

$$H_P(s) = \frac{1}{T_s+1} \tag{13}$$

The design methodology in this case is based on the IMC approach as in (Muresan et al., 2016b). The proposed fractional order IMC (FO-IMC) controller is given by:

$$H_{FO-IMC}(s) = \frac{T_s+1}{1}\frac{1}{\lambda s^\alpha+1} \tag{14}$$

where α is the fractional order. The equivalent controller of a classical control structure is computed as:

$$H_c(s) = \frac{T_s+1}{\lambda s^\alpha} \tag{15}$$

The open loop transfer function with the equivalent controller and the process transfer function is described by:

$$H_{OL}(s) = H_P(s)H_c(s) = \frac{1}{T_s+1}\frac{T_s+1}{\lambda s^\alpha} = \frac{1}{\lambda s^\alpha} \tag{16}$$

As indicated in (14), unlike the traditional IMC controller, the FO-IMC controller has two tuning parameters, the time constant λ and the fractional order α. Thus, two performance specification can be addressed: such as a settling time specification and the closed loop overshoot. In the frequency domain, these two performance criteria are translated to a specified gain crossover frequency, ω_c, and a phase margin, PM, for the open loop transfer function in (16). The specified ω_c is given in order to ensure a certain closed loop settling time, while an increased phase margin will ensure increased stability of the closed loop system. Applying the phase margin condition in (7) to the open loop system given in (16), the following relation is obtained that can be directly used to determine the value for the fractional order α, for a given value of the phase margin PM:

$$\frac{\alpha\pi}{2} = \pi - PM \tag{17}$$

Once the fractional order has been computed using (17), the time constant of the FO-IMC filter, λ, has to be determined as well. This is done by specifying the gain crossover frequency. Using now the modulus condition in (6), the time constant for the IMC filter can be determined as:

$$\lambda\omega_c^\alpha = 1 \rightarrow \lambda = \frac{1}{\omega_c^\alpha} = \omega_c^{-\alpha} \tag{18}$$

The method described above is applied to the decoupled process, defined in (12). For both transfer functions in (12), a phase margin $PM = 95^o$ is imposed. For the first loop, the gain

crossover frequency is imposed to be $\omega_c 1 = 0.01\ rad/s$, while for the second loop, $\omega_c 2 = 0.06\ rad/s$. The tuning procedure yields the following parameters: $\alpha_1 = 0.94$ and $\lambda_1 = 77.42$ for the first controller and $\alpha_2 = 0.94$ and $\lambda_2 = 14.25$, for the second one.

3. RESULTS AND DISCUSSION

The previously designed control strategies were then tested and validated under several simulation scenarios and the closed loop performance compared. In all cases, the fractional order controllers were implemented using the Oustaloup Recursive Approximation method (Oustaloup et al., 2000).

For simplicity, we present here only a few of these simulation results. A simulation of the closed loop system (considering the decentralised FO-PI control) is included in figure 1, for the two outputs of the multivariable system. These results are similar to (Palerm and Bequette, 2015). The corresponding input signals are given in figure 2. The overshoot obtained in this case is 30%, whereas the settling time is 1268s.

To test the robustness of the method, a $\pm 30\%$ gain variation is considered. The closed loop results are given in figure 3 for the mean arterial pressure and figure 4 for its corresponding input, Sodium Nitroprusside. There is a slight increase in the overshoot and the settling time due to the closed loop interactions.

Figures 5-6 show the comparison of the decentralised FO-PI control strategy with the other three control strategies that are all based on a steady state decoupling. As expected, the closed loop interaction between the loops is diminished considerably. Comparing the decentralised and decoupling FO-PI control strategies, it is obvious that the interaction is greatly reduced for the latter. Notice also a smaller overshoot (50% less), combined with a similar settling time. Using the SP control scheme allows for even better closed loop behaviour, as both the settling time and overshoot are reduced drastically when using the SP FO-PI control strategy. In the case of the SP with FO-IMC controllers, there is no overshoot and the settling time is similar to that of the SP with FO-PI controllers. A supplementary advantage comes from an even more reduced level of interaction between the control loops, making the SP with FO-IMC control the most suitable control strategy of the four algorithms tested.

A robustness test, using the SP FO-IMC-approach, consisting in $\pm 30\%$ gain variations, is presented in figure 7, for the cardiac output. There is an increase in the settling time, compared to the nominal values for the case of -30% gain variation, but the overshoot remains the same. Also, there is a slight increase in the loop interaction. Several other tests have been performed (including disturbance rejection problems) with the same conclusion: the SP with FO-IMC controllers ensures the smallest overshoot, the fastest settling time and the smallest level of interaction between the two control loops.

4. CONCLUSIONS

In this paper control of the hemodynamic state of the patient under general anesthesia. Four fractional order controllers have been designed to maintain both MAP and CO while the patient is under general anesthesia. The first hand results indicate that the proposed control strategy is suitable for this specific application and also that it can be applied in combination regulatory schemes fro better closed loop performance.

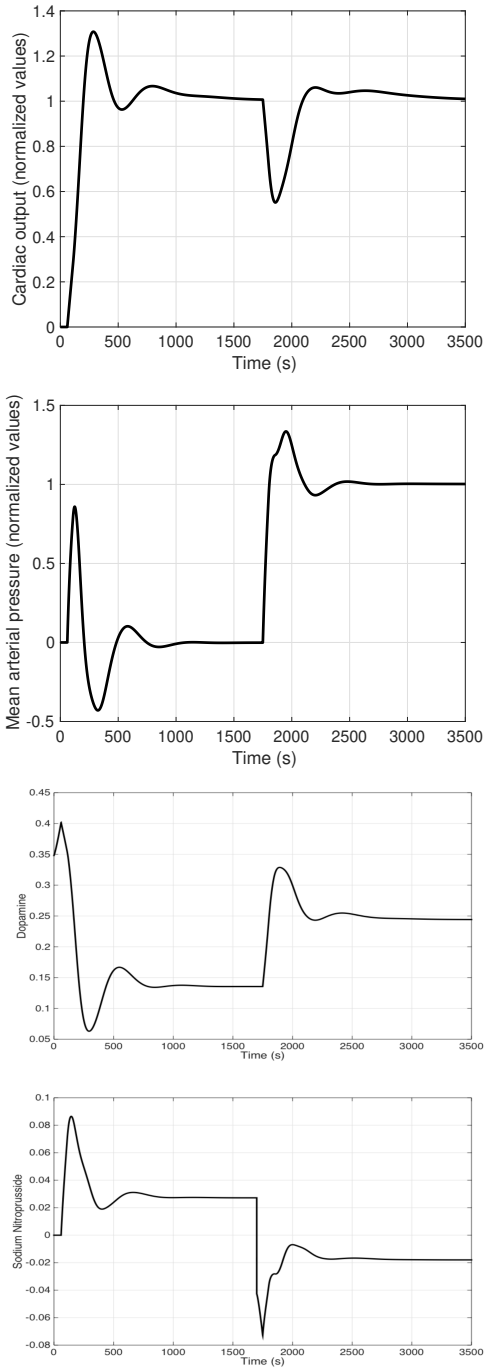

Fig. 1. Closed-loop simulation results obtained for: Cardiac Output, Mean Arterial Pressure, Dopamine input and Sodium Nitroprusside (decentralised FO-PI control).

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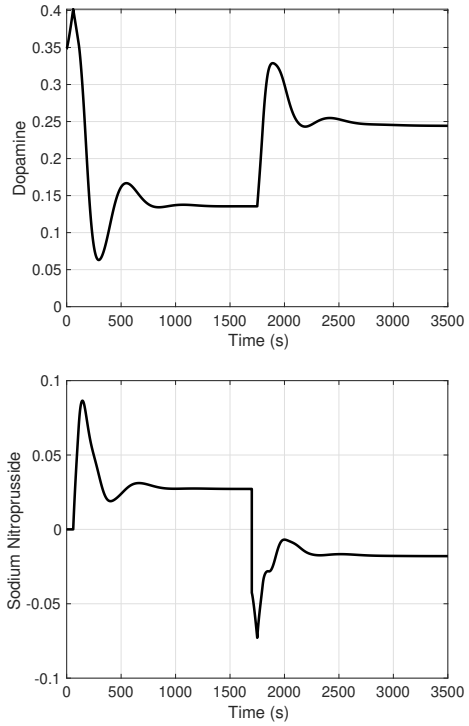

Fig. 2. Dopamine input and Sodium Nitroprusside input (decentralised FO-PI control).

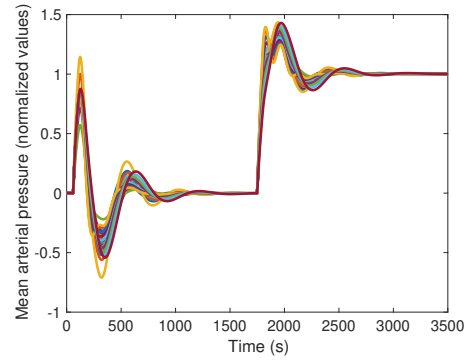

Fig. 3. Mean arterial pressure – robustness results (decentralised FO-PI control).

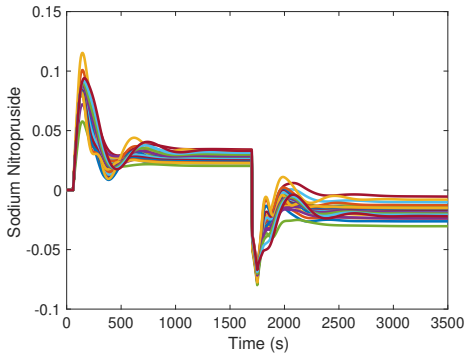

Fig. 4. Sodium Nitroprusside input – robustness results (decentralised FO-PI control).

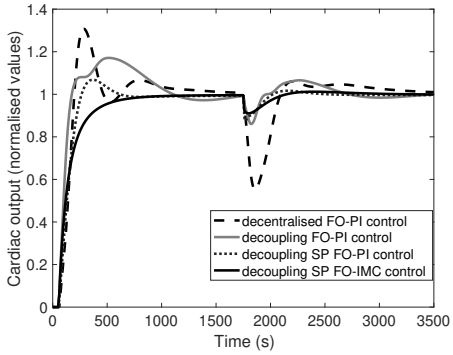

Fig. 5. Cardiac output – comparative closed loop simulation results.

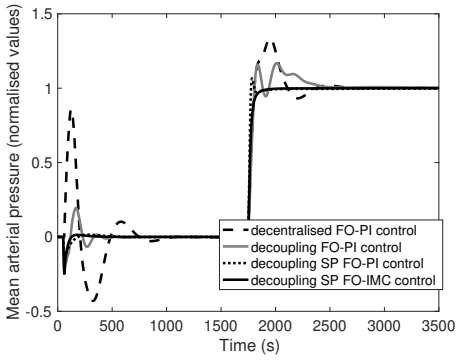

Fig. 6. Mean arterial pressure – comparative closed loop simulation results.

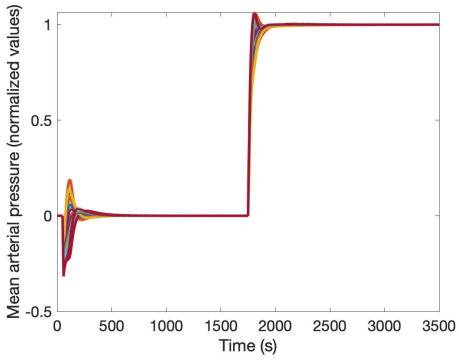

Fig. 7. Cardiac output – robustness results (SP with FO-IMC control).

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