

Robust Fractional Order PI Control for Cardiac Output Stabilisation

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Abstract: Drug regulatory paradigms are dependent on the hemodynamic system as it serves to distribute and clear the drug in/from the body. While focusing on the objective of the drug paradigm at hand, it is important to maintain stable hemodynamic variables. In this work, a biomedical application requiring robust control properties has been used to illustrate the potential of an autotuning method, referred to as the fractional order robust autotuner. The method is an extension of a previously presented autotuning principle and produces controllers which are robust to system gain variations. The feature of automatic tuning of controller parameters can be of great use for data-driven adaptation during intra-patient variability conditions. Fractional order PI/PD controllers are generalizations of the well-known PI/PD controllers that exhibit an extra parameter usually used to enhance the robustness of the closed loop system.

Keywords: cardiac output, anesthesia, intra-patient variability, fractional order controllers, autotuning method, robustness, iso-damping, stability

1. INTRODUCTION

Regulatory loops for drug dosing problems create increased awareness in the medical and engineering community, due to the slow but forward marching information technology tools into these areas. Applications vary from diabetes (Kovacs et al., 2017), cancer (Drexler et al., 2011; Kiss et al., 2013), anaesthesia (Copot and Ionescu, 2014), immunodeficiency (Popovic et al., 2015) and hormonal treatment (Churilov et al., 2009), to mention a few. As one witnesses this revolving new mechanism taking place, one begins to realize the gap between the power of today's available tools and their technological/informational potential and the state of art in medicine. Medicine is still a science in which the complexity of the patient problematic and the lack of systematic analysis and integrated tools create significant setbacks. Often, the information received by medical experts is partial and requires tedious labour to gather the correct information – often cross-fertilized among various medical services - upon a situation at hand. Sadly, this is a generic feature of today's medical practice, irrespective of the application field.

As an example, let us take a look at the anesthesia regulatory paradigm. 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 et al., 2016, 2017; Mendonca et al. 2009) and these two aspects of anesthesia are now mature for

integration in a single environment. The few closed loop studies in patients have indicated clearly the advantage of using computer control for assisting the dose management program with positive effects such as lower costs through lower medication volume per intervention and less post-intervention symptomatic side effects, thus leading to a faster recovery time for the patient (Schuttler and Schwilden, 2008). Hypnotic and opioid (analgesic medication) side-effects mark changes in other biosignals as heart rate, respiratory rate, mean arterial pressure gas in- and expiratory percentages, body temperature, etc. Hence, methods from artificial intelligence and data mining domains have proven to be useful tools, e.g. multivariate analysis (Caroll et al, 2007), fuzzy logic (Shieh et al, 2005), neural networks (Haddad et al, 2007) etc.

Rather than delivering control algorithms based on personalised patient models and optimal dosing protocols, in an effort to mimic the operation theatre with the actors playing a role, fuzzy control seemed to be a good tool at hand (Shieh et al, 2005). The fact that the controller was using a patient model based on neural network modelling with manifold of inputs to extract via nonlinear functions the response to specific drug input was clearly a step towards reality. However, we believe in the necessity to ensure stability and maintaining constraints for patient well-being and safety required a control law which can provide an analytical solution. Furthermore, feedback based control loops have a drawback in their looking backward policy, whereas true anticipatory reactions of the anaesthesiologist require predictive control techniques, i.e. looking in the future policies, and adaptation (Jin et al, 2017).

We propose in this paper to take a step forward in the paradigm and to consider the integration of the hemodynamic model for the cardiac output and mean arterial pressure. For instance, the hemodynamic model combined with sedation schemes is of great importance for cocktails of drugs as Sodium Nitroprusside, Dopamine, Propofol and Remifentanyl with unknown on the complete system. Other applications may be in the field of nanomedicine (Saadeh and Vyas, 2014), (Schulz et. al., 2009), where robots flow in the non-Newtonian environment (blood) to capture artery and veins properties (thickness, obstruction, etc). Apart from capturing biomedical data that might indicate the immediate need of drug administration, the nanorobots are also able to treat the respective area by releasing medication (Birs et. al., 2017). In order to develop efficient controllers for targeted drug delivery there are several factors, which are strictly dependent on the individual under treatment, that have to be considered in developing an accurate model of the biomedical environment (Birs et. al., 2018). In this context, due to the lack of model information, it is interesting to investigate the potential of using data-driven autotuning control methods. As being part of a large topical research community, we have already shown that emerging tools from fractional calculus are very useful to improve to a great degree the accuracy of dynamical models with respect to classical integer order modelling theory (Ionescu et al. 2017). A special case of fractional PI/PD control with automatic parameter tuning for robustness guarantee is presented here. The paper is organized as follows: the controller theoretical background is given in the next section. The model used for analysis is given in the third section, followed by the control design and results in the fourth section. A conclusion section summarizes the main outcome of this work and points to next steps.

2. ON FRACTIONAL ORDER CONTROL

Generalizations of the well-known PI/PD controllers have been developed as fractional order PI/PD (FO-PI/PD) controllers (Podlubny, 1999), with the main feature consisting in a non-integer order of integration/differentiation. As such, the FO-PI/PD controller has a supplementary tuning parameter, apart from the proportional and integral/derivative gain, common to the integer order PI/PD controllers. Due to this extra tuning parameter, FO-PI/PD controllers can be tuned to increase robustness/closed loop performance compared to their integer order counterparts. Most of the design approaches for these types of controllers imply the tuning based on gain crossover frequency, phase margin and iso-damping (Vilanova and Visioli, 2012; Muresan et al., 2015). The design is quite time consuming and involves a set of nonlinear equations that needs to be solved. An analytical solution for this set of nonlinear equations has yet to be determined. As a consequence, the solution is based on solving a nonlinear optimization problem to determine the controller parameters.

The topic of this paper is to address the tuning of fractional order PI/PD controllers and to use the extra parameter as a means to optimize the closed loop robustness to gain variations. However, the methods presented in this paper

could be modified to address the robustness to time delay variations, time constants variations, etc. The main contribution of the paper consists in the design of FO- PI/PD controllers tuned automatically, based on a simple sine test performed on the process to be controlled. This eliminates entirely the need to determine the process model, as well as solving the complicated set of nonlinear equations.

Numerous autotuning methods for classical integer order PID controllers have been developed (Åström and Hägglund, 2004; Skogestad, 2003). Among these, automatic tuning based on phase and amplitude margins (Åström and Hägglund, 1984) or on the iso-damping property (Chen and Moore, 2005) has received special interest.

A couple of autotuning methods have been developed for the design of fractional order controllers. An example is the phase shaper (Chen et al., 2004), where the design is based on the iso-damping property. A realy test is used in (Monje et al., 2008), where the autotuning procedure consists in two parts: first a design of a FO-PI controller, followed by the design of a FO-PD controller with a filter. Both parts assume the iso-damping property, a gain crossover frequency, and phase margin are the specified performance constraints. In (Yeroglu et al., 2009) the autotuning method is based on using first the Ziegler-Nichols tuning procedure to determine the proportional and integral gains of the controller, while the initial value of derivative gain is obtained using Åström-Hägglund method. Here as well, the gain crossover frequency, phase margin and iso-damping property are used to determine the fractional order controller parameters by solving system of nonlinear equations. In (De Keyser et al., 2016) the same three performance specifications are used in the autotuning procedure, but the novelty here resides in the computation of the process magnitude, phase and phase slope at the gain crossover frequency using a simple sine test on the plant via filtering techniques. Then, a graphical approach/optimization routine is used to solve the system of nonlinear equations.

In this paper an extension to fractional order controllers of a previously designed autotuning method for integer order PID controllers (De Keyser et al., 2017) is presented. The fractional order robust autotuner (FORA) is based on defining a ‘forbidden region’ that includes the -1 point in the Nyquist plane. This forbidden region is determined as a circle, based on computation of the center and radius according to a minimum phase and gain margin. Then, to ensure the iso-damping property, the integer order PID parameters of the robust autotuner are then tuned such that the loop frequency response touches the border of that forbidden region. The fractional order robust autotuning method determines the parameters of FO-PI/PD controllers, such that a certain open loop gain crossover frequency, phase margin and iso-damping are obtained. The forbidden region, in the case of the FORA, is still a circle, this time determined based on the iso-damping property and phase margin specification. The optimal FO-PI/PD controller is determined to be the controller for which the slope-difference between the circle border and the loop frequency response is minimum.

2. THE SIMPLIFIED HEMODYNAMIC SYSTEM

Within the context of drug regulatory problems, the hemodynamic system plays an important role, as it serves to bring the drug to the tissue and clear the drug from the body. It has therefore essential dynamics within the complete interactive multivariable paradigm, whatever the application.

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, 2005). 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 (De 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:

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

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.

3. CONTROLLER TUNING METHODOLOGY

To tune the fractional order PI controllers for the hemodynamic system, an autotuning method is used. The procedure attempts to determine the parameters of the FO-PI/PD controllers described by the following transfer functions:

$$C_{PI}(s) = k_p \left(1 + k_i s^{-\lambda} \right) \quad (1)$$

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., submitted). The traditional approach to tuning fractional order PI (FO-PI) controllers is performed in the frequency domain based on gain crossover frequency (ω_c), phase margin (PM) and iso-damping specifications.

The main idea of the FORA method consists in defining a circular region in the Nyquist plane that includes the -1 point as a forbidden area for the frequency response of the loop transfer function. This forbidden region, as shown in Fig. 1, is determined based on phase margin requirements:

$$C = \frac{1}{\cos(PM)} \quad (2)$$

$$R = \sqrt{C^2 - 1} \quad (3)$$

The FORA aims to determine the FORA-PI controller parameters by minimizing the following difference:

$$\min_{\lambda} \left\| \frac{dIm}{dRe} - \frac{d\mathfrak{S}_L}{d\mathfrak{R}_L} \right\|_{\omega_c}, \lambda_{\min} < \lambda < 2. \quad (4)$$

where $\frac{dIm}{dRe}$ is the slope of the circular region border,

$\frac{d\mathfrak{S}_L}{d\mathfrak{R}_L} \Big|_{\omega_c}$ is the slope of the loop $L(j\omega_c)$ frequency response at

the specified gain crossover frequency. Several optimization approaches can be employed for the minimization problem. However, a clear and simple strategy is recommended that implies taking values of λ in small increments of 0.1 and computing the value of the minimum from equation (4).

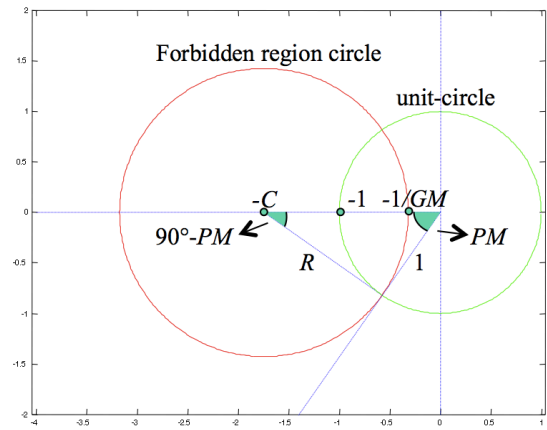


Fig. 1. Computation of the forbidden region centre and radius for the FO-KC autotuner

The condition in (4) ensures that the iso-damping property is met, for a given gain crossover frequency.

The slope of the circular region border is computed as:

$$\frac{dIm}{dRe} = \frac{\sin(PM)}{\cos(PM)} = \tan(PM) \quad (5)$$

The slope of the loop frequency response is computed as:

$$\frac{dL(j\omega)}{d\omega} \Big|_{\omega=\omega_c} = P(j\omega_c) \frac{dC(j\omega)}{d\omega} \Big|_{\omega=\omega_c} + C(j\omega_c) \frac{dP(j\omega)}{d\omega} \Big|_{\omega=\omega_c} \quad (6)$$

The right hand side of (6) can be easily computed at the gain crossover frequency by applying a single sine test of frequency equal to ω_c on the process to determine $P(j\omega_c)$ and

$\frac{dP(j\omega)}{d\omega} \Big|_{\omega=\omega_c}$ (De Keyser et al., 2016). The remaining terms

are computed as indicated next.

The frequency response of the FORA-PI controller can be easily determined using:

$$C(j\omega_c) = \frac{L(j\omega_c)}{P(j\omega_c)} = a + jb \quad (7)$$

where the loop frequency response is computed as:

$$L(j\omega_c) = M_L e^{jq_L} = \cos(-\pi + PM) + j \sin(-\pi + PM) \quad (8)$$

Given the FO-PI general frequency response:

$$C_{PI}(j\omega) = k_p + k_p k_i \omega^{-\lambda} \left(\cos \frac{\lambda\pi}{2} - j \sin \frac{\lambda\pi}{2} \right) \quad (9)$$

and equating (8) and (9) for the gain crossover frequency ω_c , the parameters of the controller are obtained as:

$$k_i = -\frac{b}{\omega_c^{-\lambda} x} \text{ and } k_p = \frac{1}{\sin \frac{\lambda\pi}{2} x} \quad (10)$$

$$\text{with } x = a \sin \frac{\lambda\pi}{2} + b \cos \frac{\lambda\pi}{2}.$$

Thus, for any small increments of the fractional order in the range $\lambda_{\min} < \lambda < 2$, the proportional and integral gains are determined according to (10). The last term in (6),

$$\left. \frac{dC(j\omega)}{d\omega} \right|_{\omega=\omega_c}, \text{ is then determined numerically.}$$

At the gain crossover frequency, (6) leads to:

$$\left. \frac{dL(j\omega)}{d\omega} \right|_{\omega=\omega_c} = \left. \frac{d\Re_L}{d\omega} \right|_{\omega=\omega_c} + j \left. \frac{d\Im_L}{d\omega} \right|_{\omega=\omega_c} \quad (11)$$

a result that allows for the computation of the slope of the loop frequency response $\left. \frac{d\Im_L}{d\Re_L} \right|_{\omega_c}$.

For all possible values of the fractional order in the range $\lambda_{\min} < \lambda < 2$, equations (6)-(11) allow for the computation of the

difference $\left\| \frac{d\Im}{d\Re} - \frac{d\Im_L}{d\Re_L} \right\|_{\omega_c}$. The robust FO-PI controller is

obtained as the one that minimizes $\left\| \frac{d\Im}{d\Re} - \frac{d\Im_L}{d\Re_L} \right\|_{\omega_c}$.

4. CONTROL DESIGN AND RESULTS

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 $PM=65^\circ$ 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.

To design the controllers, the forbidden region centre, radius, angle α and slope of the forbidden region are computed:

$$C = \frac{1}{\cos(PM)} = 2.36 \quad (11)$$

$$R = \sqrt{C^2 - 1} = 2.13 \quad (12)$$

$$\frac{d\Im}{d\Re} = \tan(PM) = 2.14 \quad (13)$$

For the first loop, a sine test of frequency ω_{c1} is performed to determine the frequency response of the first loop and its derivative. For the second loop, a similar approach is used, but with a sine test of frequency ω_{c2} . The loop frequency responses are the same for both loops, computed using (8):

$$L_1(j\omega_{c1}) = L_2(j\omega_{c2}) = -0.422 + j \cdot 0.906 \quad (14)$$

and the corresponding frequency responses of the FO-PI controllers can be easily computed based on (9):

$$C_1(j\omega_{c1}) = -0.3569 - j \cdot 0.0533 \quad (15)$$

$$C_2(j\omega_{c2}) = -0.074 + j \cdot 0.006 \quad (16)$$

and thus $a=-0.3569$ and $b=-0.0533$, for the first loop, and $a=6.68$ and $b=-11.71$, for the second loop. The FO-KC autotuning 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. A simulation of the closed loop system is included in Fig. 2 and 3, for the two outputs of the multivariable system. The overshoot obtained in this case is 30%, whereas the settling time is 1268s. These results are similar to (Palerm and Bequette, 2005). As it can be observed in Fig. 2 and 3, there is strong interaction between the two control loops.

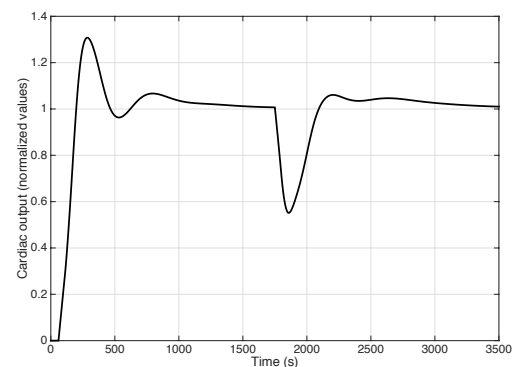


Fig. 2. Cardiac output – closed loop simulation results

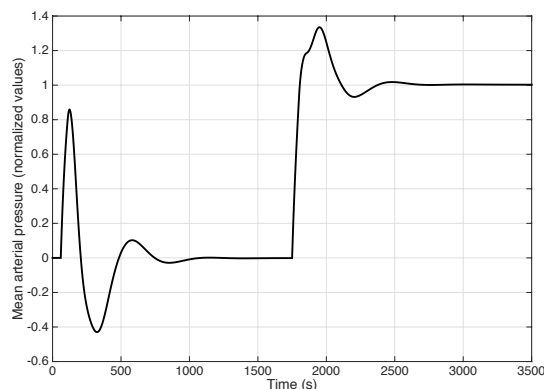


Fig. 3. Mean arterial pressure – closed loop simulation results
Further research attempts to reduce this interaction by implementing a decoupling strategy combined with FORA-PI autotuning principle. The corresponding input signals are given in Fig. 4 and 5. The normalized values are used just to prove the efficacy of the proposed control strategy. In practice, the reference signals for the arterial pressure should be a realistic blood pressure measured in mmHg, while the present study emphasizes the behavior of the closed loop system with the FOPI controller. Negative Sodium Nitroprusside control values are illustrated due to the normalization of the blue pressure that has reference value 0, which is unrealistic in real life situations.

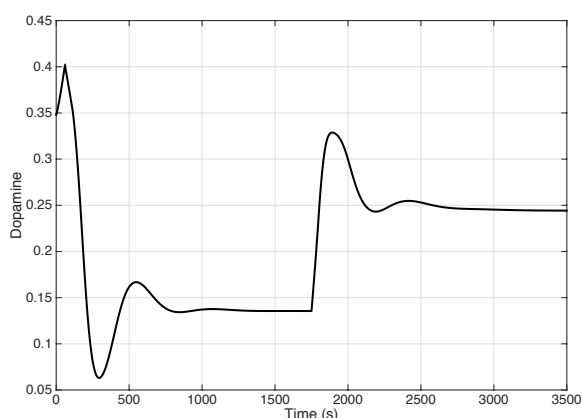


Fig 4. Dopamine input

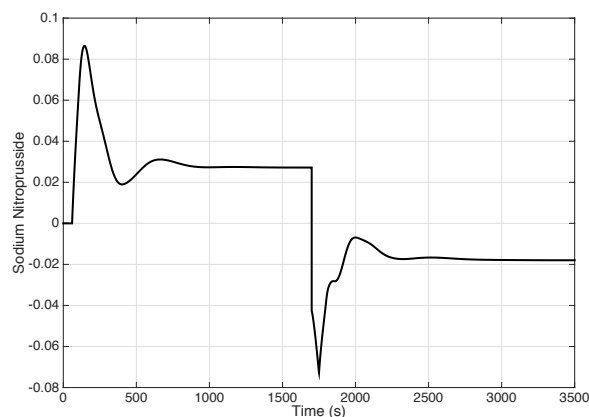


Fig 5. Sodium Nitroprusside input

5. CONCLUSIONS

In this paper, an application of hemodynamic control requiring robustness of the dynamic regulatory loop with automatic tuning of controller has been presented. The main contribution of the paper consists in that there is no need to determine the process model, neither to solve the complicated set of nonlinear equations usually required in the tuning of fractional order controllers. The method can be thus applied to data-driven information supplied to the tuning mechanism.

Next step includes the integration of this system as interacting part of another multivariable system, i.e. the general anesthesia regulatory paradigm.

ACKNOWLEDGEMENTS

This work was supported by a grant of the Romanian National Authority for Scientific Research and Innovation, CNCS/CCCDI-UEFISCDI, project number PN-III-P1-1.1-TE-2016-1396, with PNCDI III. This work was in part supported by Research Foundation Flanders (FWO) under Grant number 1S04719N.

REFERENCES

- Åström, K.J. and Hägglund, T. (1984). Automatic tuning of simple regulators with specifications on phase and amplitude margins, *Automatica*, vol. 20, 645–651.
- Åström, K.J. and Hägglund, T. (2004). Revisiting the Ziegler–Nichols step response method for PID control, *Journal of Process Control*, vol. 14, 635–650.
- Birs I., Muresan C., Folea S., Prodan O., (2017) “An Experimental Nanomedical Platform for Targeted Drug Delivery”, Australian and New Zealand Control Conference, ANZCC, Gold Coast, Australia.
- Birs I., Muresan C., Prodan O., Folea S., Ionescu C., (2018), “Analytical modelling and preliminary fractional order velocity control of a small scale submersible”, SICE International Symposium on Control Systems, Japan. (accepted)
- Caroll I., Gaeta R., Mackey S., (2007) “Multivariate analysis of chronic pain patients undergoing lidocaine infusions: Increasing pain severity and advancing age predict likelihood of clinically meaningful analgesia,” *Clin J Pain*, vol. 28(3), 702–706.
- Chen, Y.Q., Moore, K.L., Vinagre, B.M. and Podlubny, I. (2004). Robust PID controller autotuning with a phase shaper, *Proceedings of the First IFAC workshop on fractional differentiation and its applications*, 162–167.
- Chen, YQ. and Moore, K.L. (2005). Relay feedback tuning of robust PID controllers with iso-damping property, *Trans. Syst. Man. Cybern.* vol. 35, 23–31.
- Churilov A., Medvedev A., Shepeljavyi A., (2009) Mathematical model of non-basal testosterone regulation in the male by pulse modulated feedback, *Automatica*, vol. 45, 78–85
- Copot D., Ionescu C.M., (2014) Drug delivery system for general anesthesia: Where are we? *Proc. of the IEEE Int. Conf on Systems, Man, and Cybernetics (SMC)*, vol. -, 2452–2457

- De Keyser, R., Muresan, C.I. and Ionescu, C.M. (2016). A Novel Auto-tuning Method for Fractional Order PI/PD Controllers, *ISA Transactions*. vol. 62, 268-275.
- De Keyser, R., Ionescu, C.M. and Muresan, C.I. (2017). Comparative Evaluation of a Novel Principle for PID Autotuning, *Proceedings of the Asian Control Conference*, Gold Coast Australia, 1164-1169
- De Keyser R., Copot D., Ionescu C., (2015) Estimation of patient sensitivity to drug effect during Propofol hypnosis, *IEEE Int Conf on Systems, Man and Cybernetics*, Hong Kong, 2487-2491
- Drexler D., Kovacs L., Sapi J., Harmati I., Benyo Z., (2011) Model-based analysis and synthesis of tumor growth under angiogenic inhibition: a case study,” *IFAC Proceedings*, vol. 44(1), 3753–3759.
- Haddad W., Bailey J., Hayakawa T., Hovakimyan N., (2007) “Neural network adaptive output feedback control for intensive care unit sedation and intraoperative anesthesia,” *IEEE Trans Neural Networks*, vol. 18(4), 1049 – 1066.
- Ionescu C.M., De Keyser R., Torricco B., De Smet T., Struys M., Normey-Rico J., (2008) Robust predictive control strategy applied for Propofol dosing using BIS as a controlled variable during anesthesia,” *IEEE Trans Biomed Eng*, vol. 55(9), 2161–2170.
- Ionescu C.M., Machado JAT, De Keyser R., Decruyenaere J., Struys M., (2015) Nonlinear dynamics of the patient’s response to drug effect during general anesthesia.” *Comm Nonl Sci Numer Sim*, vol. 20(3), 914–926.
- Ionescu C.M., Lopes A., Tenreiro Machado J., Bates J., (2017) “The role of fractional calculus in modeling biological phenomena: A review,” *Comm Nonl Sci Numer Sim*, vol. 51, 141–159.
- Jin X., Kim C., Dumont G., (2017) A semi-adaptive control approach to closed-loop medication infusion, *Int J Adapt Ctrl and Signal Proce*, vol 31, 240-254.
- Kiss B., Sapi J., Kovacs L., (2013) Imaging method for model-based control of tumor diseases, *Proc. IEEE 11th Int. Symp. on Intelligent Systems and Informatics (SISY)*, vol. -, 271–275.
- Kovacs, L., (2017) Linear parameter varying (lpv) based robust control of type 1 diabetes driven for real patient data, *Knowledge based Systems*, vol. 122, 199–213.
- Mendonca T., Lemos J., Magalhaes H., Rocha P., Esteves S., (2009) “Drug delivery for neuromuscular blockade with supervised multimodel adaptive control,” *IEEE Trans on Ctrl Syst Tech*, vol. 17, 1237–1244.
- Monje, C.A., Vinagre, B.M., Feliu, V. and Chen, Y.Q. (2008). Tuning and auto-tuning of fractional order controllers for industry applications, *Control Engineering Practice*. vol. 16, 798–812.
- Muresan, C.I., Ionescu, C., Folea, S., De Keyser, R. (2015). Fractional Order Control of Unstable Processes: The Magnetic Levitation Study Case, *Nonlinear Dynamics* vol. 80, 1761-1772.
- Muresan C.I., Birs I.R., Ionescu C.M., De Keyser R., Existence conditions for fractional order PI/PD controllers, *Journal of Systems and Control Engineering*, submitted
- Padula F., Ionescu C.M., Latronico N., Paltenghi M., Visioli A., Vivacqua G., (2016) “Inversion-based propofol dosing for intravenous induction of hypnosis,” *Comm Nonl Sci Numer Sim*, vol. 39, 481–494.
- Padula F., Ionescu C.M., Latronico N., Paltenghi M., Visioli A., Vivacqua G., (2017) “Optimized PID control of depth of hypnosis in anesthesia,” *Comp Meth Prog Biomed*, vol. 144, 21–35.
- Palerm C., Bequette W. (2005), Hemodynamic control using direct model reference adaptive control – experimental results, *Eur J Ctrl*, vol.11, 558-571
- Podlubny, I. (1999). Fractional-order systems and PI λ D μ -controllers, *IEEE Trans Autom Control*. Vol. 44, 208-214.
- Popovic J.K., Spasic D., Tovic J., Kolarovic J., Malti R., Mitic I.M., Pilipovic S., Atanackovic T., (2015) Fractional model for pharmacokinetics of high dose methotrexate in children with acute lymphoblastic leukaemia, *Commun Nonlinear Sci Numer Simulat*, vol. 22, 451–471.
- Saadeh Y. and Vyas D., (2014) “Nanorobotic Applications in Medicine: Current Proposals and Designs”, *American journal of robotic surgery*, Vol. 1, No. 1, pp. 4– 11.
- Schulz M. J., Shanov V. N. and Yun Y., (2009) “Nanomedicine design of particles, sensors, motors, implants, robots, and devices”, Boston : Artech House.
- Schuttler J. Schwilden H., (2008) *Modern Anesthetics*. Springer: Berlin Heidelberg.
- Shieh J., Linkens D., Ashbury A., (2005) “A hierarchical system of on-line advisory for monitoring and controlling the depth of anaesthesia using self-organizing fuzzy logic,” *Eng Appl Artif Intell*, vol. 18, 307–316
- Skogestad, S. (2003). Simple analytic rules for model reduction and PID controller tuning, *Journal of Process Control*. vol. 13, 291-309.
- Yeroglu, C., Onat, C., Tan, N. (2009). A new tuning method for PI λ D μ controller, *Proceedings of the International Conference on Electrical and Electronics Engineering*. 312–316.
- Vilanova R., Visioli A, (2012), *PID Control in the third millennium*, Springer