Towards a cyber-medical system for drug assisting devices

Dana Copot[1], Robin De Keyser[1], Levente Kovacs[2], Clara Ionescu[1]

[1]Ghent University, Faculty of Engineering and Architecture, Rea search group on Dynamical Systems and Control (DySC), Technologiepark 914, B9052 Ghent, Belgium

[2] Obuda University, Physiological Controls Group, Bcsi t 96/b, H-1034 Budapest

E-mail: {dana.copot,claramihaela.ionescu,robain.dekeyser}@ugent.be
kovacs.levente@nik.uni-obuda.hu

Abstract. The purpose of this paper is to describe the role of non-integer models in healthcare pathways and how these tools provide a breakthrough in our understanding of drug delivery protocols. Two examples will be given as being typical of such applications: modeling glucose levels in diabetic type I patients and modeling pain transmission in patients suffering from (post operative) chronic pain. A wide range of tools to model these pathways and their role for use in healthcare delivery for optimal treatment and patient well-being are discussed. Individualized patient healthcare is nowadays top priority in European research framework for health and these modeling tools are primary aids in meeting these challenges.

1. Introduction

Personalized healthcare is at todays research core. Specificity of drug titration and treatment for the modern patient implies the availability, readiness of use and employment of novel tools and concepts with a background in a deep-rooted, well established clinical and medical expertise. Although as recognized still today, clinical practice is still an art rather than a science, efforts are being channeled to move from state of use to state of art. As such, state of art is far more advanced, but it lacks suitable platforms for integration, the so called cyber-physical systems, demanding hybrid sources of information processing, filtering, securing and translating into usable variables and meaningful values. A critical role of this personalized healthcare wave in current trends of research is given to the patient itself, with all its specificity, as observed from figure 1. Specificity demands the availability of individualized models, for prediction of drug effects and for steering the optimal drug titration and treatment to the patient. The goal of this paper is to bring forward the latest trends in modeling for individualized healthcare purposes. A review of state of art and state of use will be given, along with suggestions for further developments and remaining challenges.

The model is some formalized representation of the input-output relationship; mostly a mathematical model. The model will in general depend on certain parameters, such as body weight of the patient, clearance of the administered drug, etc. The adaptor is a tool to adapt the initial estimates of the parameters, whereby the controller transforms the error signal in commands for dosing. The core of feedback systems is a model of the patient with respect to the relationship between drug dosing and drug effect. Such models can be used in two directions. Using the feedforward direction it can give a prediction of the measured output. In the backwards

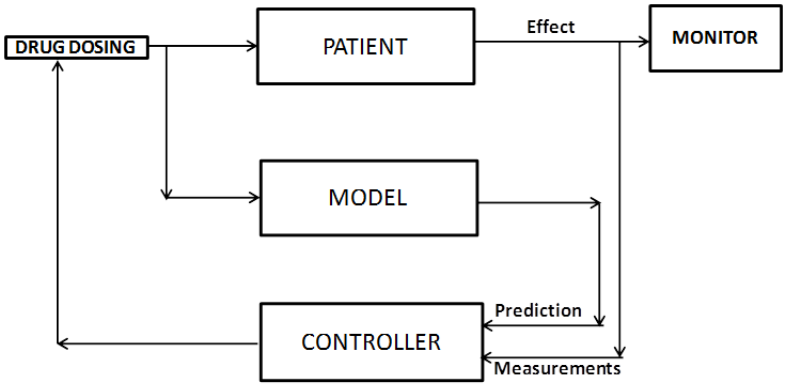

Figure 1. Block diagram of a generic model-based adaptive closed-loop system for automatic drug delivery. The closed-loop system consists of five parts: the patient, as the system to be controlled; the response that is considered as a measurable representation of the process to be controlled; a model of the inputoutput relationship, for instance a mathematical formula; and a controller, which transforms the error signal and the set-point to a drug delivery scheme

direction it can be used to determine the necessary input to achieve and maintain a certain level of the output. The paper will present two applications of such drug delivery systems: anesthesia and diabetes type I.

2. State of use

Pharmacokinetics describes the relationship between drug dose and drug concentration in plasma or the effect site. This relationship is described by processes of absorption, distribution and clearance. Notice that for intravenous drugs (e.g. anesthesia), absorption is irrelevant, so pharmacokinetic properties are described by distribution and clearance alone [1, 2].

We summarize two types of pharmacokinetic models, with prevalence for the most commonly used compartmental model. These models offer a tool for understanding the relationship between pharmacokinetics and cardiovascular physiology. The physiologic estimates are usually less accurate than fully-described physiologic models, but they represent the actual pharmacokinetics and delineate the basis for changed states of intravenous pharmacokinetics. To our knowledge, these concepts denote the inter-patient variability and intra-patient variability, which is in fact the challenging problem for optimal drug dosing [3, 4]. In principle, the altered physiological states mark a significant departure from the expected dose-response relationship, hence marked variations. Drug elimination is related to the efficiency of metabolism and/or excretion carried out by the organs of the drug elimination (e.g. liver, kidney, lung), as well as the blood flow to these organs. The two basic approaches for analyzing the effects of physiology on pharmacokinetics are the so-called forward and inverse models. With the forward model or problem, investigators estimate or measure the blood flow to each of the major organs (e.g. lungs, heart, brain, kidneys, liver, intestines) and tissue types (e.g. muscle, fat, skin) as well as the organ and tissue affinities of the drug relative to blood (i.e. tissue-blood partition coefficients). With these physiologic parameters tissue blood flow roughly represents transfer clearances between the central circulation and the tissue. The product of the tissue-blood partition coefficient and tissue masses roughly equals the volume of distribution of the drug for that tissue. Once the physiologic pharmacokinetic model is constructed, it is possible to simulate the effect of changes in tissue blood flow or cardiac output on the time course of plasma drug concentrations. Thus, physiologic models allow extrapolation outside the range of data and the existing physiologic conditions as well as interspecies scaling if the mechanisms of transport are

understood and valid. A total body pharmacokinetic model describing generic drug disposition in humans is given in figure 2 [5].

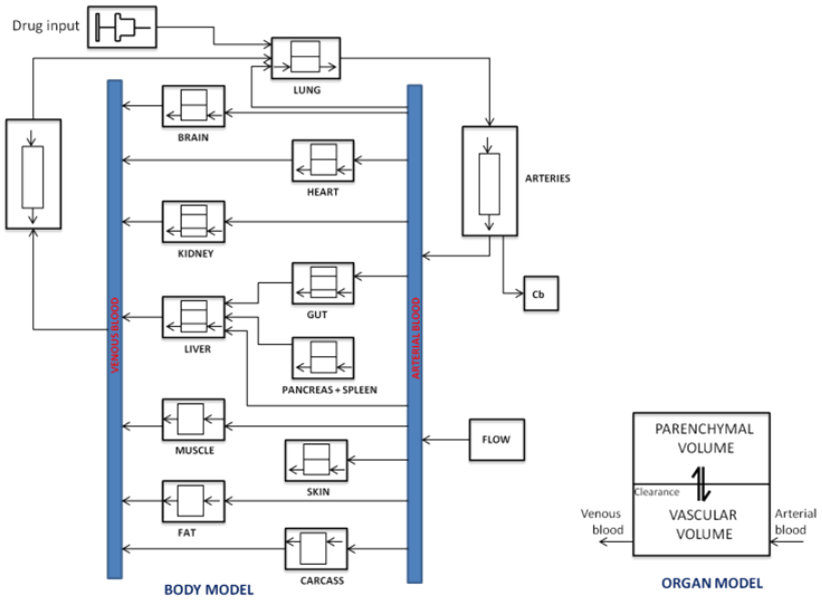

Figure 2. The total body pharmacokinetic model describing thiopental disposition in humans. The model consists of multiple tissues and blood pools connected via the vasculature and assumes venous injection and arterial blood sampling.

The inverse model is one of the most commonly de facto used in modern anesthetics and drug delivery systems in general. Only drug concentrations vs time data is drawn from blood or other tissue and fluids to create mathematical description (e.g. compartmental model), followed by derivation or more often by correlation of model parameters with physiologic measurements. This is the preferred method in humans as only time blood samples are needed for analyze and regional blood flow measurements are not required. Moreover, continuous improvement in drug measurement technology has made the acquisition of highly specific and sensitive drug concentration data from small samples sizes relatively easy. Clearance refers to the process of elimination of a substance from a volume. Distribution clearance describes the transfer of the drug between blood or plasma and the peripheral tissues. Unlike metabolic clearance, in distribution clearance the drug is not removed from the body. It is influenced by cardiac output, tissue and organ blood flow, and capillary permeability of the drug. Some pharmacokinetic parameters have precise physiologic meaning and can be used for estimates. Such progression from pharmacokinetics to physiology is considered the inverse of the forward model of taking physiologic principles and estimates to derive pharmacokinetics. Whichever way you look at it, pharmacokinetics and physiology are interwoven. Compartmental models are augmented with an extra effect-site compartment, to which corresponds an effect-site concentration [6, 7, 8]. The plasma is not the site where the drugs unfold their clinical effects. This is usually the brain, measured via EEG or evoked auditory potentials. Hence the main effect at the brain (effect site) is delayed when compared to plasma peak concentration; this is represented by adding an extra compartment (see figure 3).

The effect site is connected to the central compartment by a first order process, where the constant K0e is the rate constant for elimination of drug from the effect site. This coefficient has a large influence on the rate of rise and offset of drug effect, and the dose required to

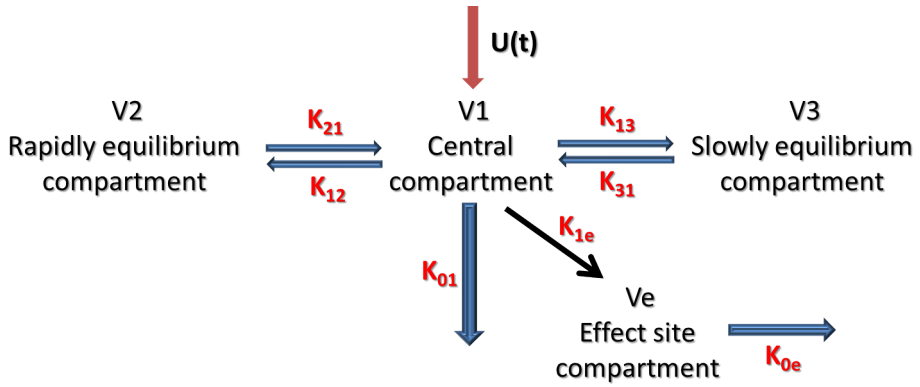

Figure 3. The addition of an effect site to a three-compartment model refers to the fact that the anesthetic effect takes place in the brain and not in the plasma. The effect site is calculated as with a negligible volume..

produce a certain drug effect. The volume of the site effect is neglected. The model in figure 3 is represented by the following set of equations.

$$\dot{q}_1(t) = K_{21}q_2(t) + K_{31}q_3(t) - K_{12}q_1(t) - K_{13}q_1(t) - K_{01}q_1(t) - K_{1e}q_1(t) + U(t) \quad (1)$$

$$\dot{q}_2(t) = K_{12}q_1(t) - K_{21}q_2(t) - K_{02}q_2(t) \quad (2)$$

$$\dot{q}_3(t) = K_{13}q_1(t) - K_{31}q_3(t) - K_{03}q_3(t) \quad (3)$$

$$\dot{q}_e(t) = K_{1e}q_1(t) - K_{0e}q_e(t) \quad (4)$$

where: u - dosing scheme as a function of time; K_{01} - rate constant reflecting all processes acting to irreversibly remove drug from the central compartment; K_{12}, K_{13}, K_{21}, K_{31}, K_{1e} - inter-compartmental rate constants [mg/l]; $V1$ - volume of the central compartment [l], V_2 and V_3 - volume of the peripheral compartments [l] (respectively muscle and fat), q_1 is the central compartment (plasma), q_2 is the rapidly equilibrium compartment (muscle), q_3 is the slowly equilibrium compartment (fat) and qe is the effect site compartment.

In daily clinical practice of general anesthesia, the goal is an individually tailored dosing of drugs, resulting in the optimal anesthetic level that is neither too light nor too deep. On the one side of the spectrum, excessively high drug doses (and inadequately deep levels of anesthesia) should be avoided to reach short recovery times and prevent excessive depression of the cardiovascular system. On the other side of the spectrum, inadequately low doses of anesthetics (and inadequately light levels of anesthesia) must be avoided to guarantee unconsciousness and prevent memory formation for intraoperative traumatic procedures (awareness). Under-dosage of anesthetics leads to conscious perception or even awareness (conscious perception with explicit memory) during anesthesia. Besides efforts to optimize anesthesia to shield the patient from stress and consequences of surgery, cost saving and issues of economy may be an issue for dosing strategies [9]. Management of anesthesia aimed at early recovery of the patient has been addressed as so-called fast track anesthesia, which nevertheless comprises much more than optimized dosing of anesthetic drugs. In this context, one challenge for the anesthesiologist is to avoid both over- and under-dosage. Therefore, knowledge of the pharmacokinetic and pharmacodynamic properties of anesthetic drugs is imperative.

The traditional form of target controlled dosing in anesthesia is by TCI [10] which was developed in the context of the development of the induction and maintenance of general

anesthesia by administration of intravenous agents only, i.e. the so called total intravenous anesthesia (TIVA) [11]. From the above scheme it becomes evident that TCI was the first formalized step that went beyond nave dosing and incorporated the dosing history into the actual dosing scheme. Thereby pharmacokinetic-pharmacodynamic models were used to estimate the present impact of doses given even far in the past on the present state of system. The first device to realize the simultaneous administration of two drugs (hypnotic and opioid) was named CATIA [12], computer-assisted titration of intravenous anesthesia. The name was chosen to underline the importance of the computer, needed for:

- tracking when/which drug was given in what amount,
- for the calculation of how much drug will still reside in the volumes of distribution in the body,
- what would be the future time course of dosing,
- maintaining a desired constant concentration in blood.

Newer developments take into account the hysteresis between blood and effect site and use the concentration at the biophase as target [13]. Inherent to model-based dosing strategies is that the model describes in general an average or typical patient. As the individual patient actually treated on the basis of this model will deviate from the average, this will translate into prediction errors with respect to the target concentrations. One approach to reduce systematic individual deviations is to take into account the dependence of the PK parameters on anthropometric data such as sex, age, weight, etc, by population pharmacokinetics [3], and to consider special patho-physiological conditions of the patient or the specific anesthetic procedure and its co-medication [14]. Another example where drug dosing represents a key role is the glucose-insulin system. The glucose-insulin control is important since glucose represents the main energy source for the brain. Low levels can affect the state of the patient (anxiety, aggressiveness, obfuscation, etc.) coma and in some cases the death. On the other hand, high glucose levels produce vascular and neural damages generating related diabetes complications (blindness, renal insufficiency, ulceration, between others). The glucose insulin regulatory system can be described as two coupled subsystems: the pancreatic system and the peripheral system. The inputs in the pancreatic system are diverse stimuli (between them the glucose level is the most important) and the output is the insulin liberated by the pancreas. In the peripheral system, the input is the insulin and the output is the glucose level. This is, there is a coupling between them: the output of one is the input for the other. The figure 4 shows the regulatory scheme. The functional relation between the two subsystems can be quantified by the rate of change of the glucose (G) and insulin (I) concentrations in time (t). The mathematical model can take the form:

$$\dot{G}(t) = f_1(G, I, t); I(t) = f_2(G, I, t) \tag{5}$$

where: functions f_1 and f_2 are characteristics of each model. Based on these relation different models have been proposed [15, 16]. A review of the mathematical modeling of glucose insulin system can be found in [17].

For the specific case of diabetic patients, the drug dosing and monitor blocks in figure 1 refer to the insulin doses and glucose monitoring respectively. The optimal route for insulin delivery is the intravenous. However, this method presents important limitations and further research has been oriented to subcutaneous pumps. Nowadays pumps technologies have become in an accepted mode of insulin therapy. However, the subcutaneous insulin delivery presents a delay between the insulin delivery and the subcutaneous absorption. This delay in general is not constant and varies inter and intra patient.

One of the key issues of the control of the glucose is the estimation of the glucose levels. An extended technique used to measure the glucose levels is Electrical Impedance Spectroscopy

(EIS). EIS is a tool that allows assessing the transfer function of a system based on an Alternate Current (AC) input voltage and the resulting AC current response. From the transfer function of the system different information regarding the behavior and structure of the system can be derived. This technique requires an identification process that relates changes in the impedance spectra with glucose changes in the biological system. An extended methodology to model those changes is based on circuit analysis where the parameters of the circuit represent a specific property in the system.

Different attempts to develop a glucose sensor based on this technique have been addressed. However, enzyme stability (enzyme immobilization, critical operating sensor conditions such as specific temperature and pH) increases the cost and limits the applications.

3. State of art

In an attempt to simplify the number of parameters in compartmental modeling, tools from fractional calculus have been employed. The fractional calculus is a generalization of integration and derivation to noninteger (fractional) order operators [15, 16]. First, a generalization of the differential and integral operators into one fundamental operator D_t^n (n the order of the operation) which is known as fractional calculus. The reason why fractional calculus should be implied in biological systems is the advantage given by the fact that it simplifies the dynamics of complex and heterogeneous systems [7, 8]. In the model presented here we considered the nonlinearity, consistency of units, mass balance and the fractional order rate constants. Considering figure 3 represented by the following equations:

$$\tau_1^{n_1-1} D^{n_1} q_1(t) = K_{21}q_2(t) + K_{31}q_3(t) - K_{12}q_1(t) - K_{13}q_1(t) - K_{1e}q_1(t) - K_{01}q_1(t) + U(t) \quad (6)$$

$$\tau_2^{n_2-1} D^{n_2} q_2(t) = K_{12}q_1(t) - K_{21}q_2(t) - K_{02}q_2(t) \quad (7)$$

$$\tau_3^{n_3-1} D^{n_3} q_3(t) = K_{13}q_1(t) - K_{31}q_3(t) - K_{03}q_3(t) \quad (8)$$

$$\tau_e^{n_e-1} D^{n_e} q_e(t) = K_{1e}q_1(t) - K_{0e}q_e(t) \quad (9)$$

where: τ_1, τ_2, and τ_3 represent the time elapsed for drug to diffuse from compartment 1, respectively compartments 2 and 3. The introduction of leads to the dimensional homogeneity of fractional rate equations, with the initial conditions $q_2(0) = d_2 = 0$, $q_3(0) = d_3 = 0$ and $q_1(0) = d_1$ =bolus injection.

A numerical solution of the general fractional differential equation $D_t^n y(t) = f(y(t), t)$ can be expressed as:

$$y(t_k) = f(y(y_k), t_k) - \sum_{j=1}^{k} c_j^n y(t_{k-j}) \quad (10)$$

where: $t_k = kh$, for k=1,2,3.N measured samples, h is the sampling period and c_j^n represent the binomial coefficient which is calculated with the following expression:

$$c_j^n = (1 - \frac{1+n}{j}) c_{j-1}^n \quad (11)$$

Applying the general solution to the set of equations 6-9, we obtain the following fractional order model describing drug diffusion in the body.

$$q_1(t_k) = (k_{21}q_2(t_k) + k_{31}q_3(t_k) - k_{12}q_1(t_k) - k_{13}q_1(t_k) - k_{01}q_1(t_k - 1))h^n - \sum_{j=1}^{k} c_j^n q_1(t_{k-j}) + u(t) \quad (12)$$

$$q_2(t_k) = (k_{12}q_1(t_k)) - k_{21}q_2(t_k))h^n - \sum_{j=i}^{k} c_j^n q_2(t_{k-j}) \tag{13}$$

$$q_3(t_k) = (k_{13}q_1(t_k)) - k_{31}q_3(t_k))h^n - \sum_{j=i}^{k} c_j^n q_3(t_{k-j}) \tag{14}$$

with: $\tau_1^{n_1-1} = \tau_2^{n_2-1} = \tau_3^{n_3-1}$, $k_{12} = K_{12}/\tau_1^{n_1-1}$, $k_{13} = K_{13}/\tau_1^{n_1-1}$, $k_{21} = K_{21}/\tau_2^{n_2-1}$, $k_{31} = K_{31}/\tau_3^{n_3-1}$, $k_{01} = K_{01}/\tau_1^{n_1-1}$and assuming $n_1 = n_2 = n_3 = n$ for simplicity. Literature reports upon several works dealing with such models [5, 6, 7, 17].

Another approach to physiologic and compartmental modeling is to use parsimonious models which lose their link to physiology, but have the advantage of less number of parameters for adaptation to the specific patient. There are several types of such models, based on both rational and non-rational input-output relationship. For applications in anesthesia, parsimonious models of rational functions have been published in [19] of the form:

$$G(s) = \frac{b_0 + b_1 s + b_2 s + \ldots b_{n_b} s^{n_b}}{a_1 s + a_2 s + \ldots a_{n_a} s^{n_a}} \tag{15}$$

with non-rational orders [20].

For applications in diabetes general rational models in the Laplace domain allow reducing the number of model parameters. However, fractional behavior of the impedance in biological systems requires solutions that increase the flexibility of the models structure maintaining a limited number of parameters [21]. For glucose sensors based EIS technique, fractional behavior in the interface electrode-electrolyte has been identified. This interface can be modeled by a structure with high number of resistors and capacitors. However, a constant phase element (CPE) can be used to model this process [22]. The CPE is a fractional equivalent electrical circuit and models an imperfect capacitor (the interface or double layer electrode electrolyte). The impedance of the CPE is calculated by:

$$Z_{CPE} = \frac{1}{Q_o \omega^{\alpha}} e^{-j\frac{\pi}{2}\alpha} \tag{16}$$

with $0 < \alpha < 1$, ω (rad/s) and Q_0 an impedance element usually consisting of a capacitance and resistance. Rational, parsimonious models use this element in order to reduce the number of parameters while increasing the flexibility of the model [21, 22]. The generic goal of such simplified models is to allow on-line identification of patients specificity by reducing the number of model parameters. With such models at hand, adaptation of control target infusion levels can be achieved as suggested for anesthesia in [23].

4. Perspectives

Current state of use in terms of TCI combined with feedback control in drug delivery systems is still based on averaged population models. In anesthesia, several studies have been reported successfully, making use of PID controllers [24, 25], nonlinear controllers [26], predictive controllers [27, 28]. In closed loop control where the glucose changes are faster than insulin absorption and action, the control algorithm should find a trade-off between slow-pace regulation well suited to mild control actions applicable to quasi-state and postprandial regulations [29]. The well-known PID controller, given its reactive action, responds to glucose changes once they occur, hence, it is necessary to develop a robust controller. However, a cautious design could not produce an effective response to meal disturbances. The most modern controllers are based on model predictive control algorithms using a model of the patient in order to

anticipate physiological actions [30, 31]. In glucose sensors based EIS, given the presence of fractional behavior, general fractional models in the frequency domain can be proposed. In [32] an approach using rational models in the Warburg variable (s) has been identified showing the reduction of the parameters and clear identification of the glucose levels compared to integer rational models. Further extension of fractional models identification in the frequency domain can be found in [33]. The challenge for the next generation of drug delivery systems can be summarized under two main trends:

- cyber-physical systems with integrated ICT platform for hybrid sources of information and monitoring devices with the aim to deliver a decision making assist device;
- integrating parsimonious models into existing platforms of TCI and feedback control systems for drug delivery systems.

The first trend involves the trans-disciplinary aspects of computer science, clinical expertise and system engineering. It requires ingenuity of integrated systems, due to the hybrid nature of various elements of such cyber-physical network. The second trend is based on system engineering concepts (identification, control, stability and robustness). For non-rational patient models, it requires moving away from the classical system theory approach. This might add challenges for stability and robustness issues, which are critical for patient safety and well-being.

Acknowledgment
C. M. Ionescu acknowledges the Flanders Research Center (FWO), grant number 12B3415N for its financial support. D. Copot acknowledges the support of the project FWO nr. G008113N.

References

[1] Absalom A., Mani V., De Smet T, Struys MRF., Pharmacokinetic models for propofol defining and illuminating the devil in the detail. British Journal of Anaesthesiology, 103, 26-37, 2009.
[2] Minto C., White M., Morton N., Kenny G., Pharmacokinetics and pharmacodynamics of remifentanil. II Model application. Anesthesiology, 86, 24-33, 1997.
[3] Schnider T., Minto C., Shafer S., Gambus P., Andresen C., Goodale D., Youngs E., The influence of age on propofol pharmacodynamics. Anesthesiology, 90, 1502-1516, 1981.
[4] Schnider T., Minto C., Gambus P., et al., The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology, 88, 1170-1182, 1998.
[5] Wada D.R., Bjrkman S., Ebling W.F., Harashima H., Harapat S.R., Stanski D.R., Computer simulation of the effects of alterations in blood flows and body composition on thiopental pharmacokinetics in humans. Anesthesiology, 87,884899, 1997.
[6] Ionescu C., Copot D., De Keyser R., Three compartmental model for propofol diffusion during general anesthesia, Discontinuity. Nonlinearity and Complexity, 2(4), 357-368, 2013.
[7] Dokomuetzidis A., Magin R., Machetas P., Fractional kinetics in multi-compartmental systems. Journal of Pharmacokinetic and Pharmacodynamic, 37, 507524, 2010.
[8] Popovic J.K., Atanackovic, M.T., Rapaic A.S., Pilipovic S., Atanackovic T.M., A new approach to the compartmental analysis in pharmacokinetics: fractional time evolution of diclofenac. Journal of Pharmacokinetic and Pharmacodynamic, 37, 119134, 2010.
[9] White P.F., Ma H., Tang J., Wender R.H., Sloninsky A., Kariger R., Does the use of electroencephalographic Bispectral Index or auditory evoked potential index monitoring facilitate recovery after desflurane anesthesia in the ambulatory setting? Anesthesiology, 100, 811817, 2004.
[10] Glen J.B., The development of Diprifusor: a TCI system for propofol. Anaesthesia, 53 [Suppl 1], 1321, 1998.
[11] Schuttler J., Kloos S., Schwilden H., Stoeckel H., Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. Anaesthesia, 43 [Suppl]:27, 1988.
[12] Schuttler J., Schwilden H., Stoekel H., Pharmacokinetics as applied to total intravenous anaesthesia. Practical implications. Anaesthesiam 38 [Suppl],5356, 1983.
[13] Schuttler J., Schwilden H., Modern Anesthetics, Berling Heidelberg: Springer, 978-3-540-72813-9, 487, 2008.
[14] Billard V., Servin F., Guignard B. et al., Desflurane-remifentanil-nitrous oxide anesthesia for abdominal surgery: optimal concentrations and recovery features. Acta Anaesthesiology Scandinavia, 48, 355-364, 2004.
[15] Oustaloup, A., La derivation non-entiere (In French). Hermes, Paris, 1995.

[16] Podlubny, I., Fractional differential equations. Academic Press, San Diego, 1999.
[17] Caumo A., Bergman R.N., Cobelli C., Insulin sensitivity from meal tolerance tests in normal subjects: a minimal model index. Journal of Clinical Endocrinology and Metabolism, 85, 4396, 2000.
[18] Breda E., Cavaghan M.K., Toffolo G., Polonsky K.S., Cobelli C., Oral glucose tolerance test minimal model indexes of -cell function and insulin sensitivity. Diabetes, 50, 150, 2001.
[19] Palumbo P., Ditlevsen S., Bertuzzi A., De Gaetano A., Mathematical modeling of the glucoseinsulin system: A review. Mathematical Biosciences, 244(2), 69-81, 2013.
[20] Dokoumetzidis A., Macheras, P., Fractional kinetics in drug absorption and disposition processes. Journal of Pharmacokinetics and Pharmacodynamics, 36, 165-178, 2009.
[21] Lemos J.M., Caiado D.V., Costa B.A., Paz L.A., Mendonca T.F., Rabico R., Esteves S., Seabra M., Robust Control of Maintenance-Phase Anesthesia, IEEE Control Systems Magazine, 34(6), 24-38, 2014.
[22] Soltesz K. Hahn J.O., Hagglund T., Ansermino J.M., Individualized closed-loop control of propofol anesthesia: A preliminary study. Biomedical Signal Processing and Control, 8(6), 500-508, 2013.
[23] Magin R., Fractals in bioengineering, Begell House Publishers, 2006.
[24] Ionescu C, Machado J.A.T., De Keyser R., Decruyenaere J., Struys M.M., Nonlinear dynamics of the patient's response to drug effect during general anesthesia. Communications in nonlinear science and numerical simulation. 20(3). 914-926, 2015.
[25] Dumont G., Feedback control for clinicians. Journal of Clinical Monitoring and Computing, 28, 511, 2014.
[26] Rocha. C., Mendonca T., Silva M.E., Individualizing propofol dosage: a multivariate linear model approach. Journal Of Clinical Monitoring And Computing, 28(6), 525-536,2014.
[27] Dumont G., Martinez A., Ansermino M., Robust control of depth of anaesthesia. International Journal of Adaptive Control Signal Processing, 23, 435-454, 2009.
[28] Ionescu C., De Keyser R., Torrico B., De Smet T., Struys MRF., Normey-Rico J., Robust predictive control strategy applied for propofol dosing using BIS as a controlled variable during anaesthesia, IEEE Transactions on Biomedical Engineering, 55, 2161-2170, 2008.
[29] 35. Krieger A., Pistikopoulos E.N., Model predictive control of anesthesia under uncertainty. Computers and Chemical Engineering, 71, 699-707, 2014.
[30] Ionescu C.M., Nascu I., De Keyser R., Lessons learned from closed loops in engineering: towards a multivariable approach regulating depth of anaesthesia. Journal Of Clinical Monitoring And Computing, 28(6), 537-546, 2014.
[31] Cobelli C., Renard E., Kovatchev B., Artificial Pancreas: Past, Present and Future. Diabetesm, 60, 2011.
[32] Kovacs L., Szalay P., Almassy Zs., Barkai L., Applicability Results of a Nonlinear Model-Based Robust Blood Glucose Control Algorithm. Journal of Diabetes Science and Technology, 7(3), 708-716, ISSN 1932-2968, 2013.
[33] Kovacs L., Szeles A., Drexler D.A., Sapi J., Harmati I., Sapi Z., Model-based Angiogenic Inhibition of Tumor Growth using Modern Robust Control Method. Computer Methods and Programs in Biomedicine, DOI:10.1016/j.cmpb.2014.01.002, 114, e98-e110, ISSN 0169-2607, 2014.