Modeling the Effect of Intravenous Anesthetics: A Path Toward Individualization

Margarida M. Silva, Alexander Medvedev, and Torbjörn Wigren
Uppsala University

Teresa Mendonça
Universidade do Porto

■ **This paper concerns** the modeling of the effect of intravenous anesthetics in the human body and is justified by the potential that individualized modeling has in the design of feedback controllers for drug delivery in clinical anesthesia. These controllers are part of a cyber–physical system (CPS) for closed-loop drug delivery in anesthesia; see Figure 1. The phenomenon (plant) to be controlled is the effect (output) of the drugs (inputs) in the human body. The controller in Figure 1a can be implemented in a personal computer, as in Figure 1b. The syringe pumps (actuators) are as shown on the left in Figure 1b and the monitors that collect the measurements from the sensors placed on the patient are shown at the top of Figure 1b.

Despite the great achievements of the last years, the potential of closed-loop controllers in the daily clinical practice is still poorly exploited. In anesthesia, even though several attempts have been made to completely automate the drug delivery to patients, no technique has become widely accepted. The mismatch between research and practice is mainly due to legal regulations. In fact, the chances of approval of any closed-loop control strategy by the regulatory entities are likely to increase with demonstration of a clinically significant safety benefit. Those benefits may encompass a reduction of the incidence of underdose- and overdose-induced complications, as compared to standard clinical practice.

One of the crucial aspects that affects the adequacy of the drug administration protocol to each patient, and consequently might determine the presence of the unwanted underdosing and overdosing, is the knowledge that the anesthesiologist has of the patient's individual response to the drug. In an automatic system, suitable models to describe the processes involved have to be formulated. On the one hand, if the purpose of the modeling is to obtain deep insight in the physiology behind the process,

Color versions of one or more of the figures in this paper are available online at http://ieeexplore.ieee.org.
Digital Object Identifier 10.1109/MDAT.2015.2452904
Date of publication: 06 July 2015; date of current version: 01 September 2015.

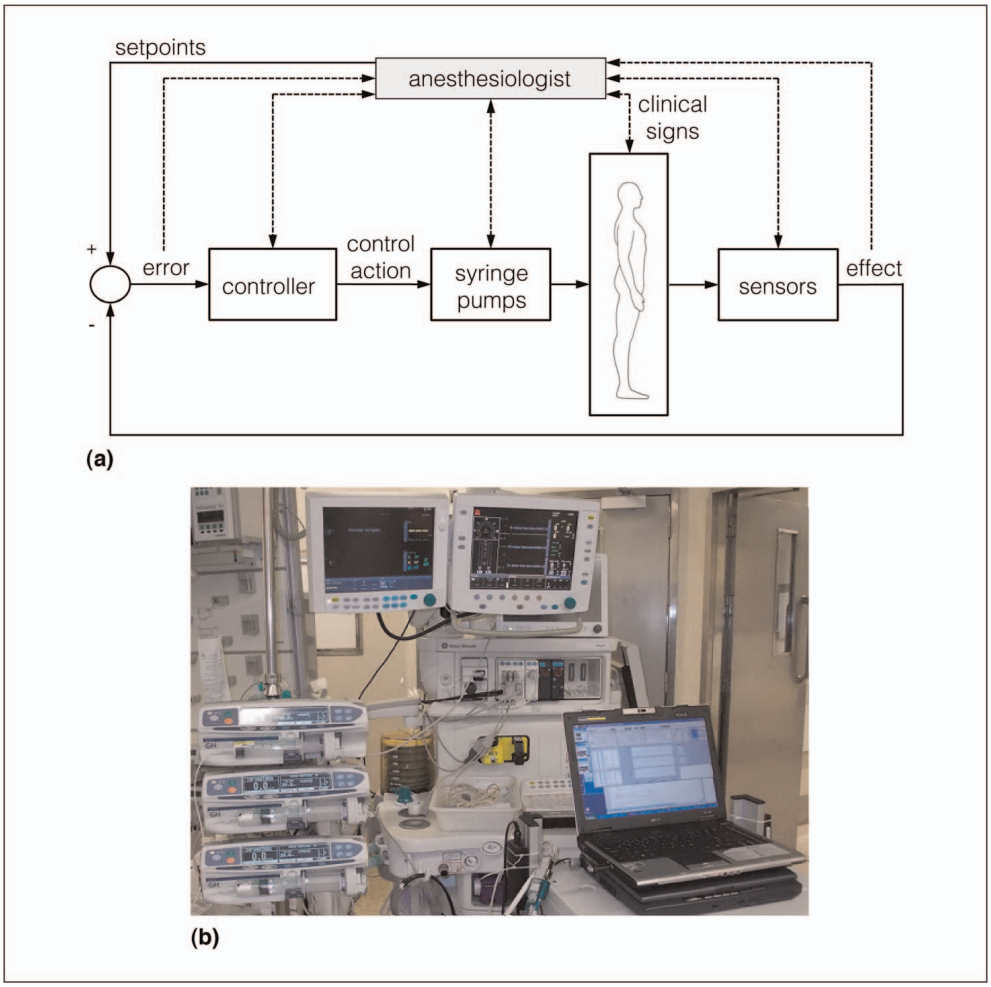


Figure 1. Cyber–physical system for drug delivery in anesthesia. (a) Schematic view of the feedback control scheme. The role of the anesthesiologist is that of a supervisor. The dashed lines depict indirect actions. The solid lines depict direct actions. The entities depicted by the arrows can be vector-valued. (b) Overview of the components of the CPS platform Galeno [17].

first principles models are usually preferred. On the other hand, in case the purpose is either prediction of the behavior of the system or model-based control, low-complexity models whose parameters are inferred from experimental data [18] are often more suitable. The modeling choice is specially important in environments that are not data-rich, or where the inputs are not allowed to be arbitrarily selected to optimize the result of identification. This is precisely the case in general anesthesia, where the administered drug doses have to comply with the intervals determined by the regulatory entities.

Furthermore, the model chosen to characterize the dynamical effect of the administered drugs on the measured physiological variables should be able to reflect variations from patient to patient, known as interpatient variability. The model should also reflect variability within the same patient under different conditions, e.g., variations in cardiac output, and/or coadministered drugs, known as intrapatient variability. This implies that the models chosen should be accurate representations of the system dynamics, being at the same time flexible enough to allow adaptation to each individual patient.

The contribution of this paper is to provide an overview of some of the models that are available in the literature for the effect of anesthetics in the human body. While first principles models have been available for 30 years (see, e.g., [5]), their use in individualized drug administration is limited. This is mainly due to the poor excitation provided by the input signals (drug doses) that does not always allow unique estimation of the model parameters. As a result, the standard first principles models for the effect of anesthetics appear to be somewhat overparameterized with respect to the available experimental data [15]. This compromises the result of system identification and effectively prevents individualized control. The discussion of model choices in this paper has model-based feedback control as end-goal, implemented as a CPS. The potential of individualization that reduced models provide via parameter estimation constitutes a crucial benefit in the field of automated drug delivery for anesthesia.

The remainder of this paper is organized in three blocks. First, the first principles models used in anesthesia are described. Second, the population models using covariates to obtain values for the model parameters are summarized. Then, recent advances in individualized modeling of anesthesia are presented. Parsimonious models suitable for online parameter

estimation and system identification methods developed for model-based individualized control are outlined. Finally, conclusions are provided.

First principles models

First principles models for the effect of anesthetics were developed based on the knowledge of the physiology of the system and using collected blood samples at different instants after the anesthetics are administered to patients. The path from the administered amount of drug to the measured effect is hence divided into two parts. First, the pharmacokinetics (PK) describes "what the body does to the drug" and concerns the drug distribution and metabolism in the blood stream. The input to the PK block is the amount of drug administered and the output is the drug blood plasma concentration. Second, the pharmacodynamics (PD) describes "what the drug does to the body." The input to the PD block is the blood plasma concentration and the output is the physiological variable that quantifies the effect of the drug. In this context, the joint effect of hypnotics and analgesics is denoted by depth of anesthesia (DoA), while the effect of muscle relaxants is denoted by neuromuscular blockade (NMB).

Supported by the experimental evidence, it is natural to model the effect of drugs in anesthesia by two cascaded blocks. Due to the fact that the majority of the PK of the drugs can be captured by linear time-invariant (LTI) dynamics, and the PD includes a static nonlinearity, a Wiener model (Figure 2) has become a popular choice.

The distribution of the drugs in the body depends on several transport and metabolic processes. Compartmental models [5] capture this behavior by considering the body divided in physiologically motivated compartments that exchange (positive) amounts of drugs between themselves. Conservation laws that assume that the total amount of drug in the system (i.e., the body including the cleared/excreted drug amount) remains constant throughout the duration of the surgery are used to derive the associated dynamics. Two or three compartmental models [5] are the ones most commonly used to describe the LTI PK of muscle relaxants, hypnotics, and analgesics.

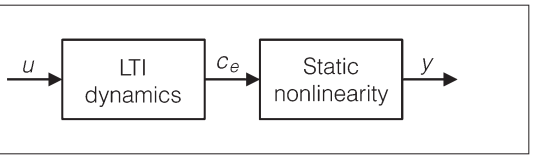


Figure 2. Wiener model: a linear time-invariant (LTI) dynamics cascaded with a static nonlinearity. The input u is the administered anesthetic, c_e is a nonmeasurable variable, and the output y is the measured effect. In general, the quantities depicted by arrows can be vector valued.

For the case of both propofol and remifentanil, a three-compartmental model is commonly used [10], assuming that, for each compartment $i, i = \overline{1,3}$ at time t, a concentration $c_i(t) = x_i(t)/V_i$ [mg ml^{-1}] of drug is present. Here V_i denotes the volume of compartment i, and x_i is the amount of drug in the same compartment. In clinical practice, the amounts of drugs in each compartment cannot be measured online. In an offline model fitting framework, it is only possible to obtain readings of the drug concentrations in the blood, i.e., in compartment 1. Assuming that $u(t)$ [mg ml^{-1} min^{-1}] is the drug infusion rate (either propofol or remifentanil), k_{10} [min^{-1}] is the clearance (rate) of the drug from compartment 1, k_{e0} [min^{-1}] is the clearance of the drug from the effect compartment, k_{ij} [min^{-1}] are transfer coefficients from compartment i to compartment j, and $c_e(t)$ [mg ml^{-1}] is the effect concentration of the drug, a state–space representation of the linear dynamic distribution of each drug in the different theoretical compartments of the human body becomes

$$\dot{x}(t) = Ax(t) + Bu(t) \tag{1a}$$

$$c_e(t) = Cx(t) \tag{1b}$$

$$A = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} & 0 \\ k_{12} & -k_{21} & 0 & 0 \\ k_{13} & 0 & -k_{31} & 0 \\ k_{e0} & 0 & 0 & -k_{e0} \end{bmatrix} \tag{1c}$$

$$B = [1 \quad 0 \quad 0 \quad 0]^T \tag{1d}$$

$$C = [0 \quad 0 \quad 0 \quad 1]. \tag{1e}$$

Model (1) accounts for the fact that blood is not the effect site of any of the intravenous anesthetics mentioned above, by connecting an additional virtual effect compartment to the central compartment. In order to ensure that the equilibrium of the PK is not affected, it is assumed that this virtual compartment has negligible volume. This constitutes the linear part of the PD model, modeled by the last row in (1c).

At the effect site, the way anesthetics act has a more involved characterization than their distribution in the body. Empirical models are therefore used to describe this part of the PD. The classic and most commonly used description is the Hill function, a sigmoid static nonlinear function relating the effect concentration of the drug with its observed effect. For the single-input–single-output (SISO) model, as for the NMB case, the static nonlinear Hill function [11] can be expressed as

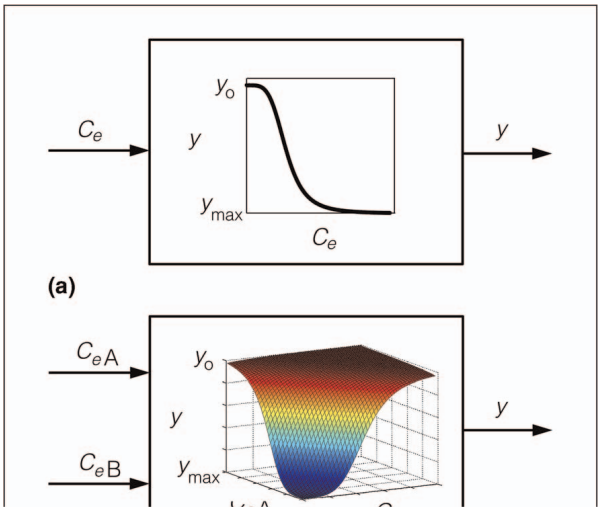
$$y(t) = y_0 + (y_{\max} - y_0)\frac{c_e^{\gamma}(t)}{C_{50}^{\gamma} + c_e^{\gamma}(t)} \tag{2}$$

where y_0 is the baseline effect when no drug is present, $y_{\max}$ is the value of the output at the maximum drug effect, C_{50} is the concentration associated with the 50% drug effect, and γ is a "sigmoidicity factor" that determines the steepness of the curve. This relation is shown graphically in Figure 3a for the SISO case with $y_0 > y_{\max}$.

For the multiple-input–single-output (MISO) case of two interacting drugs A and B, the potency of the drug mixture can be modeled as [11]

$$\phi(t) = \frac{U_{\mathrm{B}}(t)}{U_{\mathrm{B}}(t) + U_{\mathrm{A}}(t)} \tag{3}$$

where, by definition, $\phi(t)$ ranges from 0 (drug A only) to 1 (drug B only).



(a) SISO case and (b) MISO case. The *y*'s denote the outputs and the c_e's denote the inputs to the nonlinearity.

To calculate (3), both effect concentrations $c_{e\mathrm{A}}(t)$ and $c_{e\mathrm{B}}(t)$ are first normalized with respect to their concentration at half the maximal effect ($C_{50\mathrm{A}}$ and $C_{50\mathrm{B}}$, respectively) as

$$U_{\mathrm{A}}(t) = \frac{c_{e,\mathrm{A}}(t)}{C_{50\mathrm{A}}} \quad U_{\mathrm{B}}(t) = \frac{c_{e,\mathrm{B}}(t)}{C_{50\mathrm{B}}}. \tag{4}$$

The nonlinear concentration–response relationship for any ratio of the two drugs can then be described by the generalized Hill function

$$y(t) = y_0 + (y_{\max} - y_0)\frac{\left(\frac{U_{\mathrm{A}}(t)+U_{\mathrm{B}}(t)}{U_{50}(\phi(t))}\right)^{\gamma}}{1 + \left(\frac{U_{\mathrm{A}}(t)+U_{\mathrm{B}}(t)}{U_{50}(\phi(t))}\right)^{\gamma}} \tag{5}$$

where y_0, $y_{\max}$, and γ are as defined before, and $U_{50}(\phi(t))$ is the number of units associated with 50% of the maximum effect of both drugs at ratio $\phi(t)$. This relation is shown graphically in Figure 3b for the MISO case with $y_0 > y_{\max}$.

In [11], the quadratic polynomial

$$U_{50}(\phi(t)) = 1 - \beta\phi(t) + \beta\phi^2(t) \tag{6}$$

with $\beta > 0$ was proposed for the expression of $U_{50}(\phi(t))$ for the case of the synergistic interaction between propofol and remifentanil.

Because the majority of the indices used to measure the effect of propofol and remifentanil are bounded from below by zero, $y_{\max} = 0$ should be considered. For instance, the patient-dependent parameters in the propofol–remifentanil-induced DoA standard model are hence the following seventeen: $k_{10\mathrm{p}}, k_{12\mathrm{p}}, k_{13\mathrm{p}}, k_{21\mathrm{p}}, k_{31\mathrm{p}}, k_{e0\mathrm{p}}$, for propofol, $k_{10\mathrm{r}}, k_{12\mathrm{r}}, k_{13\mathrm{r}}, k_{21\mathrm{r}}, k_{31\mathrm{r}}, k_{e0\mathrm{r}}$, for remifentanil, and $C_{50\mathrm{p}}$, $C_{50\mathrm{r}}$, γ, β, and y_0.

Population models

The question on whether the PK parameters in (1) for propofol and remifentanil correlate with, e.g., age, sex, and height of the patients arose after the pioneering trials of automatizing the drug delivery to patients under anesthesia. The method to obtain population models relies on regressions made on obtained as empirical Bayesian estimates, based on a prior using no covariates. In the second step, the individual PK/PD parameter estimates are regressed

on the covariates using a generalized additive model. In the third and final step, the software NONMEM is used to optimize the population model [7]. This approach was used in, e.g., [10] for the Minto population model of remifentanil.

When it comes to propofol models for adults, the Marsh model and the Schnider model [14] are the most well known and used in the clinical practice, particularly in the so-called target controlled infusion (TCI) devices; see, e.g., [1]. The TCI devices implement open-loop control approaches to drug delivery. The anesthesiologist, based on the status of the patient and on the progress of the anesthetic procedure, sets the target concentration (setpoint) and the TCI device calculates the corresponding drug profile to be administered by inverting the linear part (1) of the PK/PD model. The target can be either set at the blood or the effect concentration. The parameters k_{ij} in (1) are estimated based on population model distributions, using the relationships in, e.g., [14] for the case of propofol, or in [11] for the case of remifentanil.

The predictive performance of the aforementioned models for a population of adults was assessed in several studies; see, e.g., [1, Table 4] for a summary. An average population underprediction of 20% in the blood concentration of propofol using the Marsh model and an average overprediction of the measured remifentanil concentration by 15%, with an average inaccuracy of 20% were found. It should be noted that, even though being capable of explaining the variability of responses in a population, these models are not tailored to capture each individual response to the anesthetics, and may give higher inaccuracies when used in an individualized model-based control framework.

Regarding the nonlinear PD, the work in [9] proposes a population distribution for the parameters γ, β, and C_{50} in nonlinear interaction (4)–(6). Again, these parameters are not individualized, but rather population based and, to the authors' knowledge, no study with covariate regression has been published for the case of the propofol and remifentanil PD. In common clinical practice in using TCI, these nonlinear interaction parameters are usually inferred from the signs that are collected from the patient, and based on the clinicians' expertise.

Individualized models

Before the beginning of a general anesthesia procedure, the only information that is available about the patient are his/her weight, height, sex, and clinical history. Even though providing guidelines, none of these, unfortunately, gives an accurate picture of how the patient will react once the intravenous anesthetics are administered. However, with the progress of the surgery, more and more data become available to characterize each patient's individual response to the administered drug. It is then natural to conjecture that methods that learn the response of the patient to the administered drug online can provide valuable information to characterize the individual response to the anesthetics. This is the idea behind recursive system identification [18].

As shown in [15], the standard PK/PD models described in Section II seem to be overparameterized for the case of NMB and DoA, considering the input signals (drug doses) commonly administered in the clinical practice. On the one hand, the bolus dose (that may be seen as a pulse of a finite amplitude) that is administered in open loop during the induction phase yields rich information on the nonlinearity. On the other hand, the information collected during closed-loop operation is limited to a certain point of nonlinearity, corresponding to the setpoint. Naturally, more information about the dynamics of the system may be collected instead, but the closed-loop feedback signal is poorly excitatory. This is particularly troublesome because the input signals are subject to the clinical protocols and cannot be freely chosen to facilitate a better performance of the system identification methods.

The work in, e.g., [16] proposes minimally parameterized Wiener models for the effect of intravenous anesthetics. The models keep the Wiener structure of the PK/PD ones and were developed using real data. The two main observations that motivated the development of these models were as follows.

First, the linear dynamics of the standard models are, considering the data available, "practically" overparameterized. The sensitivity and identifiability work in [15] provided insights on which parameters are poorly identifiable given the typical administered drug doses. Further, in some cases, the linear part of the model exhibits nearly pole-zero cancellation, which indicates a need for model reduction while keeping the same cascade structure of the model. The fact that the Wiener model structure is retained still allows for some physical connection to the standard PK/PD models and facilitates, e.g., the interpretation of the system identification results.

Second, the Wiener structure provides the system with enough nonlinear behavior, while enabling, e.g., inversion of the nonlinearity. It is therefore relatively simple to use for both identification and individualized closed-loop control.

The minimally parameterized model for the propofol–remifentanil DoA is shown here to exemplify the modeling idea. In [16], a third-order continuous-time model was proposed for the linear dynamics of both propofol and remifentanil. The transfer function of the linear dynamic part of the Wiener model for propofol is given by

$$G_p(s) = \frac{\chi}{s+\chi}\frac{d_1\chi}{s+d_1\chi}\frac{d_2\chi}{s+d_2\chi} \tag{7}$$

that may be realized in a state–space form as

$$x(t) = Ax(t) + Bu(t) \tag{8a}$$

$$c_e(t) = Cx(t) \tag{8b}$$

$$A = \begin{bmatrix} -d_2\chi & 0 & 0 \\ d_1\chi & -d_1\chi & 0 \\ 0 & \chi & -\chi \end{bmatrix} \tag{8c}$$

$$B = [d_2\chi \quad 0 \quad 0]^T \tag{8d}$$

$$C = [0 \quad 0 \quad 1]. \tag{8e}$$

The parameters $d_i, i = \overline{1,2}$, are determined offline using previously collected real data and are chosen to be constant and equal to 9 and 10, respectively [16]. The individualization parameter to be estimated online is $\chi > 0$.

The state–space model equivalent to (8) for the case of the NMB was shown to be a compartmental model [5]. This is an important feature of a model for drug delivery because it allows, e.g., the development of compartmental control laws, as in, e.g., [17].

The transfer function of the linear dynamic part of the Wiener model for remifentanil is similarly given by

$$G_r(s) = \frac{\eta}{s+\eta}\frac{l_1\eta}{s+l_1\eta}\frac{l_2\eta}{s+l_2\eta}. \tag{9}$$

The parameters l_i, $i = \{1,2\}$, are determined offline from historical data and are chosen to be equal to 2 and 3, respectively [16]. The individualization parameter to be estimated online is $\eta > 0$. The transfer function given by (9) may be realized in state–space form similarly to (8).

Using the standard model in (5) as a starting point, and considering $y_{\max} = 0$ for the case of most of the DoA indices, a new formulation for the MISO nonlinearity (5) was proposed in [16] as

$$y(t) = \frac{y_0}{1 + \left(\frac{y_r(t)}{C_{50r}} + m\frac{c_{ep}(t)}{C_{50p}}\right)^{\zeta}} \tag{10}$$

where m and ζ are individualization parameters and y_0 is set depending on the monitoring device in use, and C_{50p} and C_{50r} are propofol and remifentanil normalizing constants, respectively [16], that are fixed and nonpatient dependent.

From this, the patient-dependent parameters in the DoA minimally parameterized model are hence the following four: χ, η, m, and ζ. Due to this low number of parameters, efficient recursive parameter estimation methods could be developed, as in, e.g., [16]. With the online parameter estimation, the accuracy of the obtained models for each individual is better than when population models were used; see, e.g., [8].

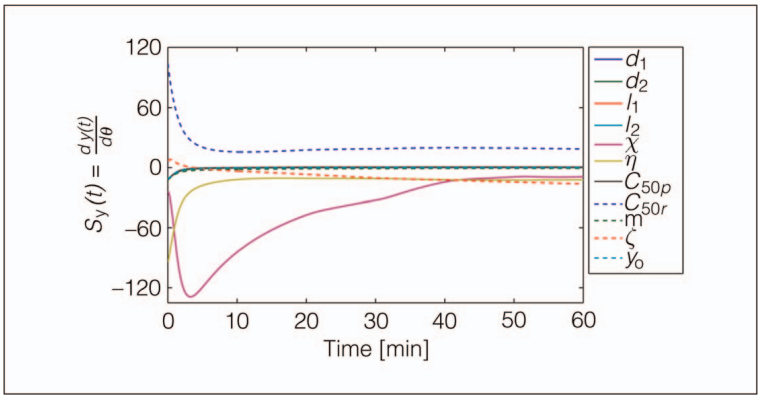


Figure 4. Output sensitivity function with respect to the model parameters for the propofol–remifentanil DoA minimally parameterized model (adapted from [15]).

Online parameter estimation

The sensitivity and local identifiability analysis in [15] revealed useful information on the potential of both the first principles models and the minimally parameterized models in providing reliable parameter estimates for closed-loop controller design. Results show that, e.g., for the case of the first principles model for the propofol–remifentanil DoA, five parameters from the LTI blocks (1) and C_{50r} and ζ from the nonlinearity (2) may not be identifiable, given the input excitation that is commonly present in the clinical practice. On the other hand, the results in Figure 4 show that the output is highly sensitive to the parameters χ, η, m, and ζ. Singular value

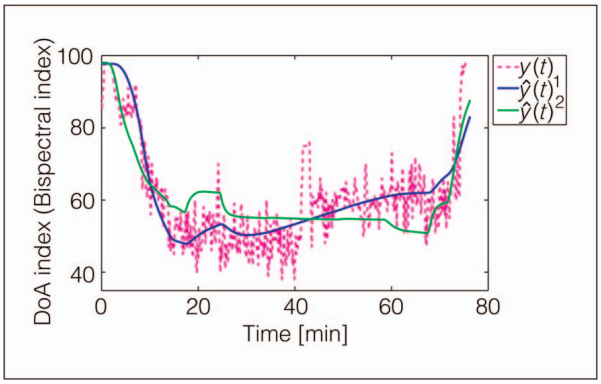


Figure 5. Batch identification results for case number 16 in the database in [8]: the measured BIS is in pink dashed line; the predicted BIS using the minimally parameterized model is in blue solid line; the predicted BIS using the first principles model is in green solid line (results from [8]).

decomposition of the sensitivity matrix (see [15, Table 7, App. B]) confirms the choices of χ, η, m, and ζ as the parameters to be estimated in the minimally parameterized model.

Also, the results of [8] can be used to illustrate the difference in predictive performance of the first principles models and the minimally parameterized models for the DoA. In Figure 5, it is clear that the prediction using the minimally parameterized model outperforms the prediction using the first principles models. Both the initial transient and the global trend of the signal are better captured by the blue solid line, meaning that the individualization via parameter estimation is likely to be more accurate if the minimally parameterized models are used in the estimation algorithms.

The minimally parameterized model was also used for the development of adaptive model-based controllers; see, e.g., [17]. The control scheme was made adaptive by the use of the online parameter estimates provided by an extended Kalman filter (EKF). The reference tracking results are promising and encourage the continuing use of the proposed controller in the clinical practice.

In spite of the good results in closed loop obtained with the EKF, owing to the nonlinear nature of the system, it is expected that estimation algorithms making direct use of the nonlinear model perform better than estimation methods that rely on linearization. In [13], the minimally parameterized Wiener model for the NMB was therefore estimated with a particle filter (PF) and the estimation accuracy was compared with that obtained by the EKF. It was shown that the PF outperforms the EKF when it comes to convergence rate, bias, and tracking capability. Using the parameter estimates obtained by the PF, the intrapatient variability of the model is quantified. The results strongly indicate that the variability in the nonlinear PD part of the model is higher than that of the linear part. Note that the computational complexity of the PF is higher than that of the EKF. This, however, is not an issue in this application since the sampling rates of the signals are limited by the monitoring devices, e.g., 1/20 s for the case of the NMB or 1/5 s for the case of the DoA.

The performance of an individualized feedback controller is, in fact, directly influenced by the intrapatient variability. The presence of a high intrapatient variability in the estimated models further supports the use of the minimally parameterized models for estimation toward individualized drug delivery in anesthesia.

Some successful clinical cases of closed-loop drug delivery with individualized estimation of the parameters of the minimally parameterized model can be found in, e.g., [17]. As shown in the upper plot of Figure 6a, the NMB of a patient was controlled to the setpoint via the administration of the drug rate in the bottom plot in Figure 6a. The estimates of the model parameters are shown in Figure 6b. For the SISO NMB case, consider $m = 0$ in (10).

While the linear design of controllers operating around the almost linear region of the Hill function could sometimes be sufficient, it would most likely not guarantee performance under changes in the patient's dynamics. Also, the question on whether nonlinear phenomena such as sustained oscillations may appear due to the introduction of a controller in the loop needs to be considered [21]. The research in [21] is supported by the clinical evidence of oscillatory behavior in the literature for cases of closed-loop drug delivery in anesthesia. The results of [21] provide mathematical support to the clinical findings. The bifurcation analysis in [21] shows that, for the case of proportional–integral–derivative (PID)-controlled NMB, complex nonlinear behavior such as sustained oscillations may indeed appear under certain conditions, as a consequence of Andronov–Hopf bifurcation phenomena. These oscillations result in underdosing and overdosing of anesthetics, and should therefore be avoided. An expression for

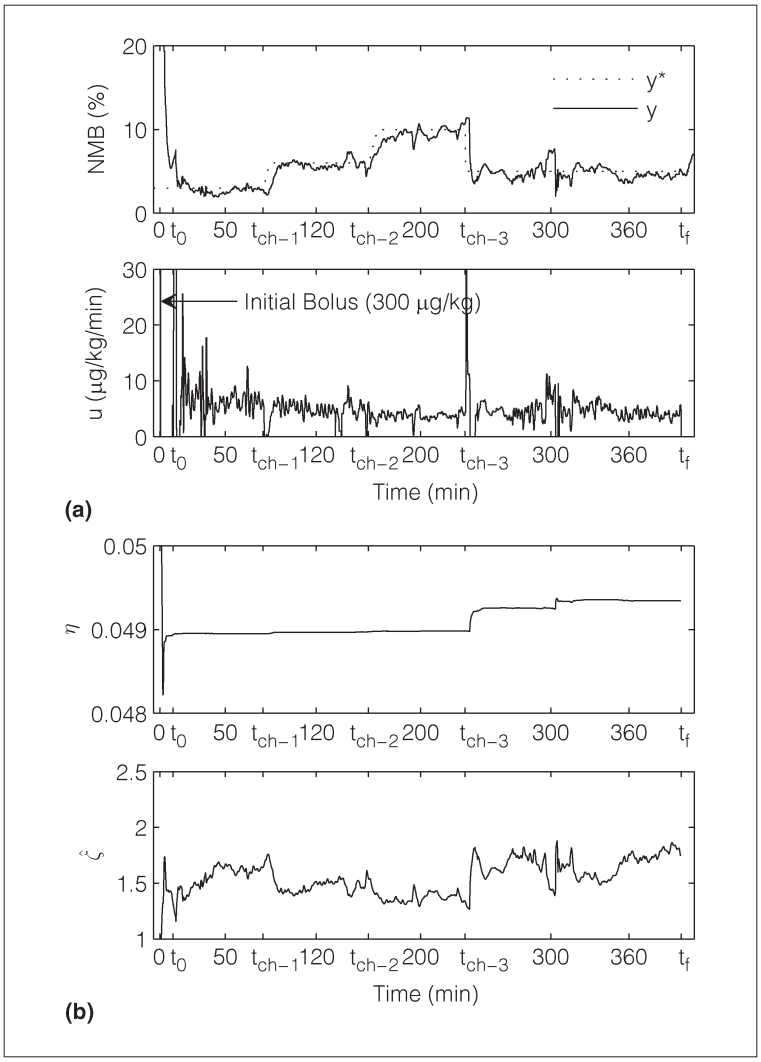


Figure 6. Real closed-loop control results using the minimally parameterized model for individualization of drug delivery administration for the NMB (adapted from [17]). (a) Upper plot: controlled NMB *y* and reference y^*. Bottom plot: control input (rocuronium infusion rate). (b) Upper plot: estimates of parameter η. Bottom plot: estimates of parameter ζ.

the distance to such bifurcation is also suggested in [21], giving rise to a way of monitoring how far the closed-loop system is from sustained nonlinear oscillations and thus quantifying the risk of the latter events. Even though a PID controller designed based on an individualized Wiener model [21] can initially ensure a safe distance to bifurcation, the model parameters sometimes drift close to a critical zone as the surgery proceeds. The latter has been demonstrated on clinical data in [13] by estimating the distance to the Andronov–Hopf bifurcation by means of parameter estimation with a PF.

Provided that estimation of the model parameters is performed, the PID tuning scheme in [22] ensures that the closed-loop operating point of the drug delivery system is moved away from the region of oscillatory dynamics by changing the controller gains in a systematic way. The proposed tuning allows the closed-loop system to recover from oscillations that were previously observed in clinical trials and that led to underdosing and overdosing of the administered drug. By introducing a time-varying proportional PID gain, the type of equilibrium remains the same as in the case of constant controller gains. This is desirable since no additional complex nonlinear behavior is introduced by this tuning [22].

Other models with reduced complexity

Several other papers advocating low complexity modeling for the effect of intravenous drugs in anesthesia have also appeared in the literature recently.

For the case of the NMB, the idea of using a simple model was exploited in, e.g., [2]. In [2], a logarithmic transformation was applied to the model output and, based on real data, a linear relationship between the effect concentration of the muscle relaxant atracurium and the transformed output variable was suggested.

In [6], a simplified linear MISO interaction model for the effect of propofol and remifentanil in the bispectral index (BIS) is proposed. The reasoning behind this simplification is that, in the intensive care unit (ICU), the BIS levels are inside a 40–60 window, which is the region where the interaction surface described by (5) is assumed to reduce to a plane [6]. The use of this linear model in a model-based controller should however be performed with some caution during, e.g., the induction phase, where the BIS signals typically decrease from a value close to 100 to 30. Additional safety nets should be considered in that case. The time delay in the linear MISO relationship in [6] is estimated online by a method proposed by the same authors. The first-order plus time-delay (FOPTD) block of the FOPTD–Hill model in [19] also considers an explicit delay that is identified after the initial 8 min of the induction phase. Nevertheless, the minimal output error-norm representation in [19] shows that, for the considered data, the model is unidentifiable along a path in the time-delay/Hill parameter space representation.

More recently, a reduced model for the hypnosis–remifentanil-induced DoA with only four parameters

was proposed in [20] and its performance compared with other complex model structures.

The number of models with low complexity and the successful closed-loop control strategies using these models that can now be found in the literature are strong indicators that model reduction is a correct path toward individualization of drug delivery to patients under anesthesia.

CPS for drug delivery

As mentioned at the beginning of this paper, the introduction of a CPS for drug delivery in daily clinical anesthesia has to be preceded by rigorous testing procedures to ensure its safe operation.

On the one hand, the predictive performance of the models with a reduced number of parameters is likely to be higher than that obtained with the standard overparameterized models. Therefore, outliers and fault detections, aspects that are critical in closed-loop, would also be more reliable and safer. Monitoring functions to ensure that no nonlinear phenomena like sustained oscillations arise in the loop should also be part of the CPS.

On the other hand, the importance of reliable interfaces is unquestionable. Related to this, anesthesia control over wireless interfaces is a likely future development. There are many scenarios, e.g., natural catastrophes, disasters, and war, when one could benefit from such functionality. One may consider situations when medical staff without detailed knowledge of the field are forced to serve as anesthesiologists. A plausible solution would then be to let the medical staff handle the actuator and the sensor in the control loop discussed in this paper. The controller and support functions could be remote and connect with the local actuator/sensor node over wireless interfaces. In that way, one central control unit could serve perhaps hundreds of ongoing operations simultaneously. The actuator and sensor could, e.g., be integrated in a dedicated smartphone and the current cellular networks could be employed to provide the wireless interface.

There are a number of issues that then would need a further study. Wireless protocols for machine-to-machine communication would need development. These protocols would have to tailor, e.g., the bit error probability of the transmission to levels tolerable by the closed-loop anesthesia application. The capacity and the area coverage of the service would have to be optimized as well. Here it deserves to be mentioned that a reduced required closed-loop bit rate would be beneficial for coverage, a fact that can be understood by considering the possibility to do repetition coding. It would probably be advisable to consider the knowledge collected in the field of networked control systems during the last 15 years; see, e.g., [3], [4], and [12].

This paper provided an overview of the models used for the effect of intravenous anesthetics, spanning from first principles models to low complexity parsimonious ones that were recently proposed. The lesson learned is that system identification models, with reduced complexity, enable an accurate and individualized characterization of the behavior of the system, via online estimation of the model parameters. This capability is crucial and should be used when the design of closed-loop controllers for automated drug delivery to patients under anesthesia is the end goal, implemented as a CPS. ■

■ References

[1] A. R. Absalom and M. M. R. F. Struys, *Overview of Target Controlled Infusions and Total Intravenous Anaesthesia*, 2nd ed. Gent, Belgium: Academic, 2007.

[2] H. Alonso, T. Mendonça, J. M. Lemos, and T. Wigren, "A simple model for the identification of drug effects," in *Proc. IEEE Int. Symp. Intell. Signal Process.*, Budapest, Hungary, Aug. 2009, pp. 269–273.

[3] J. Baillieul, "Feedback designs for controlling device arrays with communication channel bandwidth constraints," presented at the ARO Workshop Smart Structures, Aug. 1999.

[4] J. Baillieul and P. J. Antsaklis, "Control and communication challenges in networked real-time systems," *Proc. IEEE*, vol. 95, no. 1, pp. 9–28, Jan. 2007.

[5] K. Godfrey, *Compartmental Models and Their Application*. New York, NY, USA: Academic, 1983.

[6] C.-M. Ionescu, R. De Keyser, and M. M. R. F. Struys, "Evaluation of a propofol and remifentanil interaction model for predictive control of anesthesia induction," in *Proc. 50th IEEE Conf. Decision Control/Eur. Control Conf.*, Orlando, FL, USA, Dec. 2011, pp. 7374–7379.

[7] J. W. Mandema, D. Verotta, and L. B. Sheiner, "Building population pharmacokinetic-pharmacodynamic models. I.

Models for covariate effects,'' *J. Pharmacokin. Biopharmaceut.*, vol. 20, no. 5, pp. 511–528, 1992.

[8] T. Mendonça, H. Alonso, M. M. Silva, S. Esteves, and M. Seabra, ''Comparing different identification approaches for the depth of anesthesia using BIS measurements,'' in *Proc. 16th IFAC Symp. Syst. Identif.*, Brussels, Belgium, Jul. 2012, pp. 781–785.

[9] M. J. Mertens et al., ''Propofol reduces perioperative remifentanil requirements in a synergistic manner: Response surface modeling of perioperative remifentanil propofol interactions,'' *Anesthesiology*, vol. 99, no. 2, pp. 347–359, Aug. 2003.

[10] C. F. Minto et al. ''Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development,'' *Anesthesiology*, vol. 86, pp. 10–23, 1997.

[11] C. F. Minto et al. ''Response surface model for anesthetic drug interactions,'' *Anesthesiology,* vol. 92, no. 6, pp. 1603–1616, 2000.

[12] G. N. Nair and R. J. Evans, ''Stabilization with data-rate-limited feedback: Tightest attainable bounds,'' *Syst. Control Lett.*, vol. 41, no. 1, pp. 49–56, 2000.

[13] O. Rosén, M. M. Silva, and A. Medvedev, ''Nonlinear estimation of a parsimonious Wiener model for the neuromuscular blockade in closed-loop anesthesia,'' in *Proc. 19th IFAC World Congr.*, Cape Town, South Africa, Aug. 2014, pp. 9258–9264.

[14] T. W. Schnider et al. ''The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers,'' *Anesthesiology,* vol. 8, no. 5, pp. 1170–1182, May 1998.

[15] M. M. Silva et al., ''Local identifiability and sensitivity analysis of neuromuscular blockade and depth of hypnosis models,'' *Comput. Methods Programs Biomed.*, vol. 113, no. 1, pp. 23–36, 2014.

[16] M. M. Silva, T. Mendonça, and T. Wigren, ''Online nonlinear identification of the effect of drugs in anaesthesia using a minimal parameterization and BIS measurements,'' in *Proc. Amer. Control Conf.*, Jun. 2010, pp. 4379–4384.

[17] M. M. Silva, L. Paz, T. Wigren, and T. Mendonça, ''Performance of an adaptive controller for the neuromuscular blockade based on inversion of a Wiener model,'' *Asian J. Control*, 2014. [Online]. Available: http://dx.doi.org/10.1002/asjc.981

[18] T. Söderström and P. Stoica, *System Identification*. London, U.K.: Prentice-Hall, 1994.

[19] K. Soltesz, ''On automation in anesthesia,'' Ph.D. dissertation, Dept. Autom. Control, Lund Univ., Lund, Sweden, Sep. 2013.

[20] H. Wolf et al., ''Online process identification of hypnosis,'' in *Proc. IEEE Int. Conf. Syst. Man Cybern.*, Manchester, U.K., Oct. 2013, pp. 2225–2230.

[21] Z. T. Zhusubaliyev, A. Medvedev, and M. M. Silva, ''Bifurcation analysis of PID controlled neuromuscular blockade in closed-loop anesthesia,'' *J. Process Control*, vol. 25, pp. 152–163, 2015.

[22] Z. T. Zhusubaliyev, M. M. Silva, and A. Medvedev, ''Automatic recovery from nonlinear oscillations in PID-controlled anesthetic drug delivery,'' presented at the 15th Eur. Control Conf., Linz, Austria, Jun. 2015.