GALENO: Computer aided system for modeling, monitoring, and control in anesthesia

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Abstract
This article presents a real-time software platform (the GALENO platform) that was designed to support the development of algorithms to automate anesthesia procedures. Automation of anesthesia can contribute to improve the anesthesia practice, by personalizing health care, and by allowing the anesthesiologist to concentrate on supervisory tasks, avoiding repetitive manual work that can be executed and optimized by using automatic control systems. The GALENO platform is used for rapid prototyping of new control algorithms applied to anesthesia and was developed to be used by medical staff as a supporting tool for general anesthesia in a clinical setting. It has been tested in simulation and in real clinical settings. The platform can control the administration of several anesthetic drug combinations for total intravenous anesthesia using the DoA/BIS index and the NMB level, during induction and maintenance phases. To highlight some of the main features of the platform, and its practical results, two control algorithms are used as examples, the closed-loop predictive min–max target controlled infusion is described and is used to control DoA/BIS, and a self-tuning proportional-integral-derivative is used to implement the control of the NMB.

KEYWORDS
anesthesia automation, biomedical simulation, control system, DoA/BIS index, neuromuscular blockade, TCI

1 | INTRODUCTION

General anesthesia is a controlled medical procedure applied during a surgery, consisting in the administration of anesthetic drugs, inhaled and/or intravenous, to patients. The specific drugs keep the patient in a reversible adequate state of hypnosis, amnesia, analgesia, muscle relaxation, and abolition of reflexes. The process is performed with permanent supervision of the anesthesiologist that must keep track of the patient’s physiological signals and their trends to decided the adequate drug doses. This may cause a high workload and a high level of stress on the anesthesiologist that depends on the variability of the patient’s characteristics. Inadequate drug administration, under doses or over doses, may result in complicated situations to the patient. Automation of anesthesia helps by allowing the anesthesiologist to concentrate on the supervisory tasks, and freeing her/him from executing repetitive tasks that can be optimized by using automatic control systems to compute and to adjust the drug doses.
The GALENO platform\textsuperscript{1} is a software platform for research and development of anesthesia automation. It was designed to facilitate the rapid prototyping of new control algorithms (off-line mode) and to allow clinical specialists to gain experience on using (closed-loop) automatic control of anesthesia in real-time. This requires a period of training in using the platform, usually involving the team.

In real-time mode, it provides access to physiological variables and commands syringe pumps. It allows users to develop and run control algorithms without imposing a specific controller structure or type. Depending on the functionalities/algorithms implemented by the users, a controller can have constant parameters, adaptive parameters by performing online identification, or even manual adjustment of parameters. The aim is to hide the complexity involved in data communication, data extraction, data validation, error recovering, user interface programming, data storing and retrieving, and to expose a simple standard interface that facilitates the design, the implementation and the testing of new control algorithms. It was developed in the GALENO project,\textsuperscript{1} with the experience obtained from the IDEA project\textsuperscript{2} using the HIPOCRATES Software Package,\textsuperscript{3} and the experience on scientific results achieved in several research projects related to the topic of anesthesia, performed by the Department of Mathematics, Faculty of Sciences at University of Porto, and INESC-ID of Lisbon Portugal.\textsuperscript{4-7} The platform communicates with the DATEX/Ohmeda anesthetic monitor to acquire biomedical/physiological and with syringe pumps to define and to validate drug perfusion rates. This platform is used to process physiological data and to perform pharmacokinetic/pharmacodynamic model identification.\textsuperscript{8-10} The models obtained from the identification process are used to expand the normalized (GALENO) database and to improve the characterization the patient population. This is used in computer simulation to development and to evaluate new control algorithms that will be available in the platform\textsuperscript{11-13} for simulation and training and for real-time control.\textsuperscript{14} To facilitate the rapid development of the platform and the implementation of new control algorithms, the MatLab software is used, but due to the high cost of the MatLab software, it may be seen as a constraint. The design of the user’s platform interface and the implementation of the GALENO platform, incorporate the requirements defined by anesthesiologists from the hospitals: (i) Hospital Santo António - Centro Hospitalar do Porto and (ii) Hospital Pedro Hispano - Unidade Local de Saúde de Matosinhos, both in Porto, Portugal, that evaluate the operational use of the platform. This cooperation allowed a strong exchange of experiences and important practical criteria definition to be used for validating the GALENO platform in real clinical environments.

In the recent work,\textsuperscript{15} a software anesthetic simulator based on Matlab is described. It has similar aspects to the Galeno platform. The Galeno platform uses Matlab, it has the off-line mode, for simulation, for control strategies development (DoA and NMB) and, to explore other physiological signals.

In the survey\textsuperscript{16} a concise overview on the recent evolution of closed-loop anesthesia is presented, several platforms for real-time control of anesthesia (McSleepy, iControl, Infusion Toolbox 95, RUGLOOP II, CONCERT-CL, CLADS) are briefly described. The majority of them use proportional-integral-derivative (PID) controllers or target controlled infusion (TCI). In the case of the Galeno platform, is able to perform real-time control in a clinical environment and, the models and the controllers are not restricted by the platform design. This article describes the structure of the Galeno platform and present results obtained with it. This article does not have the objective to present a review of the literature on control of anesthesia. However, it is important to develop control strategies that are robust.\textsuperscript{14} For a review on the literature, other works\textsuperscript{14,16-18} should be considered.

The contribution of this work consists in the development of the GALENO platform for fast prototyping of new control algorithms, its validation through simulation and clinical results, that can be used by medical staff as a support tool for general anesthesia in a clinical setting. The practical results show that it fulfills the requirements for computer controlled administration of anesthesia supervised by an anesthesiologist, and can be used as a tool to support training.

The article is organized in six sections. Section 2 presents an overview of the main topics for automation of anesthesia. Section 3 describes the methodology and the requirements used to develop the Galeno platform. Section 4 describes the architecture of the GALENO platform including the functionalities, operating modes and the system expansion capabilities. Section 5 illustrates the usefulness and feasibility of the GALENO platform to work in clinical setting as research anesthetic control tool. Two exemplifying controllers: (i) closed-loop control predictive min–max TCI for DoA-hypnosis (BIS index) with the drug propofol and (ii) autotuning PID controller for NMB control with the drug rocuronium are shown. Finally, conclusions are drawn in Section 6.

\textsuperscript{1}https://www.fc.up.pt/galeno/
2 | BACKGROUND

Induction, maintenance and recovery are the main phases of general anesthesia. During these phases two indices are usually employed that help the anesthesiologist to assess the state of the patient during a general anesthesia. The hypnotic component of Depth of Anesthesia (DoA-hypnosis) level can be evaluated with the bispectral index (BIS),\textsuperscript{19} that is a multifactorial parameter derived from the electroencephalogram. It is a dimensionless number that varies from 0 to 100, where 0 represents the total suppression of cortical electrical activity, and 100 represents the full cortical electrical activity. A BIS between 40 and 60 is associated with a low probability of intraoperative awakening and awareness, and is recommended for general anesthesia.

The peripheral nerve stimulator and the train-of-four (TOF) method are used to determine the degree of residual muscle activity in the presence of neuromuscular blocking agents,\textsuperscript{20} to facilitate safe tracheal intubation, immobilization during the surgery and, at the end of the anesthesia, to decide the moment to perform a safe tracheal extubation. TOF consists of four consecutive supramaximal stimuli with an interval of 0.2 s that are delivered along the path of a nerve, and the response of the muscle (thumb adductor muscle), its contraction is measured to evaluate the NMB. The GALENO platform uses the first response (T1%) of the TOF method to monitor and control the patient’s neuromuscular blockade. In this method, the T1 is calibrated by a reference twitch, usually at the ulnar nerve at the wrist,\textsuperscript{21} that is performed before the administration of the neuromuscular blocking drug. A value of 10 is normally used as a reference for the NMB. Figure 1 represents a typical time evolution response to TOF stimulation.

The interaction between a drug and the human body is described using the concepts of pharmacokinetics (PK) and pharmacodynamics (PD). The PK describes the drug concentration time course in the sampled body fluid, normally plasma, serum or the blood, resulting from the administered dose.\textsuperscript{22} Several methods can be used for modeling purposes, in particular, the PK compartmental parametric models are very useful for the control design. The number of compartments and the way how they are connected depend on the drug/effect to be modeled. Figure 2 shows a general diagram of a compartmental model.

The central compartment is usually associated with organs with a high blood supply/flow. Peripheral compartments are associated with organs with a lower blood flow. The number of compartments defines the structure of the mathematical model and is selected by trial and error, the parameters of the model ($k_{12}$, $k_{21}$, …) define the dynamic behavior of the model, and are estimated using statistical methods that fit the output of the model to real data (drug concentration

**FIGURE 1** Typical response of Neuromuscular Blockade with the train-of-four method using a nondepolarizing drug (e.g., Rocuronium or Atracurium)

**FIGURE 2** Schematic representation of parametric pharmacokinetic model with three compartment and the effect compartment
obtained from blood samples taken periodically during an essay). From the automatic control point of view, the important aspect is to consider the compartment model as a whole that is described by a set of differential equations. The mathematical model that is associated with the schematic representation shown in Figure 2 is given by

\[
\frac{dC_1}{dt} = \frac{IR - (k_{10} + k_{12} + k_{13})V_1 C_1 + k_{21} V_2 C_2 + k_{31} V_3 C_3}{V_1} \\
\frac{dC_2}{dt} = \frac{k_{12} V_1 C_1 - k_{21} V_2 C_2}{V_2} \\
\frac{dC_3}{dt} = \frac{k_{13} V_1 C_1 - k_{31} V_3 C_3}{V_3} \\
\frac{dC_e}{dt} = k_{30} C_1 - k_{30} C_e,
\]

where the state variables and the constants are described by: \(k_j\): is the Transfer rate from compartment \(i\) to \(j\) (min\(^{-1}\)), \(V_i\): is the Volume of the compartment \(i\) (ml), \(C_1\): is the Plasma concentration (DQ/ml), \(C_2\), \(C_3\): are the Peripheral compartment concentrations (DQ/ml), \(C_e\): is the effect site concentration (DQ/ml) \(IR\): is the drug infusion rate (DQ/ min). They provide continuous description of the blood concentration and are used as input to the PD model.

Examples of this class of models are the compartmental models proposed by Marsh,\(^{23}\) Schnider,\(^{24}\) and Mintz\(^{25}\) and Gepts,\(^{26}\) for propofol, remifentanil, and sufentanil. The GALENO platform has implemented the four models to predict the effect site concentration of the respective drug and other dynamic models. The PD model relates the concentration provided by the PK model (or measured) and the observed drug effect. Typically, the Hill function,\(^{27}\) that is a nonlinear static function, is used to described the observed effect and the drug concentration in the effect site.

\[
y(t) = \frac{C_e}{C_{so} + C_e(t)},
\]

where \(C_e\) represents the drug concentration at the effect site, \(C_{so}\) represents the drug concentration to obtain 50% of the maximum effect, and \(y\) describes the slope of the Hill function.

3 | METHODS AND PLATFORM REQUIREMENTS

The Galeno platform was developed using a top-down methodology where the general/operational requirements were first defined with the information and help provided by the team of anesthesiologists working in the project. The main requirements are listed next:

1. The GALENO platform should run on personal computers with Microsoft Windows operating systems;
2. It must have two modes of operation, the real-time mode for DoA and NMB closed-loop control, and the off-line mode for research purposes, modeling, identification, control design, and database update;
3. In real-time mode, it must plot graphical data, plots of controlled variables (DoA, NMB) and drugs flow rates, and process the commands of the user;
4. It must communicate with the anesthetic equipment, syringe pumps, and anesthesia machine as represented in Figure 3;
5. In real-time mode, every 5 s, the platform must request and process the information from the anesthesia machine (Datex-Ohmeda), that contains the biomedical signals, and must communicate, test and command the syringe pumps;
6. Safety procedures must be implemented to avoid drug overdoses and under doses. In this case, syringe pump state information and alarm mechanisms must be used together with supervision algorithms to set warnings and alarms;
7. In real-time mode, it must store raw data in a database to be used later, either to check the operation of the platform or when the platform is used for model identification and control design;
8. In real-time mode, it must run a DoA controller with a sampling time of 5 s and a NMB controller with a sampling time of 20 s;

\(^{2}\)DQ represents the measurement unit of the drug quantity: ng, µg, or mg.
9. In real-time mode, at any instant, if necessary, the anesthesiologist can take control of the syringe pumps and command them manually.

Based on the list of requirements a development plan and a testing plan were defined to implement a strategy of separation of concerns corresponding to the following operation modes:

1. Online data acquisition from the syringe pumps and from the anesthesia machine;
2. Syringe pumps manual command to manipulate drug flow rate and/or to apply a bolus;
3. Closed-loop control of NMB and BIS.

Assessing the correctness of the software and the time constrains associated with the operation of the platform in real-time mode are critical for the operation of the platform. Meaning that, the actions corresponding to data acquisition, data processing, computation of the control action, and syringe pump commanding must be performed during the time intervals described by the requirements. This is assessed using timers and software check-points and time logs that are produced by the application. It must be emphasized that the present platform implements a soft real-time system, small time jitter, or a missed time deadline can be compensated by the closed-loop control algorithms.

Collection of clinical data have been performed from patients that undergo elective surgery in accordance to the applicable legislation and good ethical practices.

4 | GALENO PLATFORM ARCHITECTURE

Based on the above requirements, the GALENO platform was structured in a stack of functional layers, where each layer exposes a well-defined programming interface and hides the function implementations. With this approach a function from a layer can be modified without affecting other software layers. The functional layers where organized in two application-components the GALENO-data acquisition drivers (GDAD) and the GALENO-monitoring and control of anesthesia (GMCA).

The GDAD is used only in real-time mode, it implements a communication abstraction between the GMCA and the devices, such as the anesthesia machine and syringe pumps, that have their particular communication protocols. The GDAD handles communication errors and implements recovering and backup procedures to avoid unsafe application shutdowns. It was developed using the computer programming language C-Sharp. The “DATEX-Ohmeda”,28 “ALARIS-GH-Pump”,29 and “B-Braun-Compact-Pump”30 communication drivers, are included in GDAD. New drivers can be included as needed. The time required for exchanging data between the PC and the anesthetic devices, using serial communication, becomes the most difficult demand that GDAD must handle. For example, the data message of DATEX-Ohmeda monitor with the patient biomedical data has more than 600 bytes, using a baud rate of 19,200 bit/s it
Figure 4  Functional architecture of the GALENO platform

<table>
<thead>
<tr>
<th>Operation mode</th>
<th>Functions to perform</th>
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<tbody>
<tr>
<td>Off-line mode</td>
<td>1. Filtering, decoding, and input/output synchronization for BIS and NMB, 2. Model identification and simulation for DoA/BIS and NMB dynamics, 3. Controller design and simulation for DoA/BIS and NMB, 4. GALENO database management.</td>
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Table 1  Summary of GALENO platform operation modes and functions

Takes approximately 312 ms to receive the message. In addition, the system must consider the response time of anesthetic equipment and the possibility transmission errors during the communication.

The GMCA application is the core of the GALENO platform, it was developed using the MATLAB platform (Version 7.9.0.529, R2009b, win32) to allow fast software prototyping and to facilitate the access to mathematical software and methods that are necessary to implement model identification and control algorithms.

The GMCA can be used in real-time mode together with the GDAD application for real-time control of DoA and NMB or for monitoring. Figure 4 shows the functional architecture of the GALENO platform, that is designed to handle the two operating modes, where reusability of software and the reliability of the data exchange between the two operation modes were considered. Table 1 summarizes the two operating mode functions.

4.1  GMCA: Working in off-line mode

To work in off-line mode, GMCA provides a set of functions with the following purposes: (i) process all the information acquired from each patient; (ii) manage the GALENO Database of PK/PD models of DoA/BIS and NMB; (iii) simulate new methods for identification, modeling and control, and (iv) e-training in anesthesia procedures. GMCA also integrates DoA/BIS and NMB simulators.

4.2  GMCA: Working in real-time mode

In real-time mode, the main function of GMCA is to aid the anesthesiologist during a general anesthesia. Execution time is monitored to assess that temporal constraints are not violated. In the test of the GALENO platform in real-time
mode, using a personal computer with AMD microprocessor at 2.2 GHz and 1 GB RAM Memory, the average CPU time consumption was much less than 5 s, that is the fastest sample time of the DoA controller. The anesthesiologist, and in order to use the GMCA, must configure the application according to the following steps:

1. Communication configuration and testing.
2. Input the patient’s data and the anesthesia specifications (gender, age, weight, height, type of surgery, sensors, date, and so forth). The patient’s parameters (gender, age, weight, and height) are usually used by the control algorithms. The remaining data are used for statistical purposes.
3. Input of the anesthetic drug specifications.
4. Configure the automation module for TIVA, Figure 5.
5. Interact with the application using the GUI of GMCA in the real-time mode, Figure 6).

4.3 Expanding the GALENO platform

Given the large number of commercial anesthetic devices and the wide variety of anesthetic protocols the GALENO platform presents an expandable architecture that includes the following items:

(i) the control algorithms for DoA/BIS and NMB;
(ii) the GALENO Database and models generated by the GALENO platform and
(iii) the anesthetic device drivers (Biomedical monitor and infusion pumps).

This is accomplished by using a specific directory tree where all valid Matlab functions or GDAD are placed. The GALENO platform automatically recognized these functions or programs that can be used according to the platform setting.
FIGURE 6 GUI of GALENO monitoring and control in real-time mode controlling the NMB with rocuronium (pump 1) and BIS with propofol (pump 2), and remifentanil (pump3)

5 | GALENO PLATFORM UTILIZATION AND TESTING

In the framework of anesthesia practice two approaches emerged, the administration of a bolus to increase the drug concentration in the central compartment, and the administration of the maintenance perfusion rate. TCI has been accepted to facilitate the work of the anesthesiologists to control the DoA with intravenous anesthesia, this implies the use of special syringe pumps. Other control methods have been proposed. The main idea of TCI is to use a predefined PK model (compartmental model) to predict the plasma or and effect site concentration, and to compute the quantity of drug that must be administrated to obtain the target concentration value. It must be emphasized that the TCI is an open-loop control strategy where the anesthesiologist closes the control loop by changing the reference value of the TCI controller based on her/his evaluation of the patient’s DoA state.

In this article, as an example of using the GALENO platform for rapid prototyping of a new control algorithm, the development of a closed-loop TCI controller is presented based on the concept of predictive control. For this purpose standard remote controlled syringe pumps are used. A cascade control architecture is used to control DoA. The inner controller is the predictive TCI controller, that adjusts the infusion rate of the propofol based on the target concentration value (reference value) that it provided by the external controller (PI controller). The external controller is employed to compute the target concentration reference based on the tracking error computed from the BIS index. The NMB control is demonstrated with an autotuning PID controller that adjusts the muscle relaxant infusion rate based on the real NMB and the NMB reference.

5.1 | Predictive min–max TCI

The TCI controller is designed in discrete time using the predictive control framework with a state space representation (3) obtained from the Schneider model, using the zero-hold method with a sampling time $Ts = 5/60$ (time constants in [min]),
\[ x(k + 1) = A_d x(k) + B_d u(k) \]  
\[ y(k) = C_d x(k), \]

where \( k \) represents the discrete time, the state vector is \( x(k) = [C_1(k) \, C_2(k) \, C_3(k) \, C_4(k)]' \), \( y(k) \) represents the output to be controlled and \( u(k) \) represents the input, the drug administration that must be manipulated. \( A_d, B_d, \) and \( C_d \) are matrices, with adequate dimensions. The Schnider model does not provide information about the level of parameter uncertainty. It turns out that, it is considered a perfect representation of the drug (propofol)/patient dynamics. Defining \( N \) as the predictive horizon and iterating (3) from \( k + 1 \) to \( k + N \), it is possible to describe the output \( y(k) \) as a function of the future control values \( u(k + j) \) with \( j \in [0, N - 1] \) and the current state \( x(k) \). If the additional constraint is imposed \( u(k + i) = 0 \) for \( i \geq 1 \) to \( N - 1 \), then

\[ y(k + i) = C_d A_d^i x(k) + C_d A_d^{i-1} B_d u(k), \]

This strategy reflects the notion that in order to have a fast change of the drug concentration at both the central compartment and at the effect site, the drug must be applied quickly and not distributed along a “large” time interval. This approach is used with a receding horizon control strategy in the sense that only \( u(k) \) is used at time \( k \) with the control algorithm being applied at time \( k + 1 \) to compute \( u(k + 1) \). The aim is to select the value for \( u(k) \) such that a fast reference tracking is obtained but without output overshoot, that is \( y(k + i) = C_{\text{ref}}(k) \) (concentration target) for a future time instant \( k + i \). The reference is assumed constant along the control horizon interval and equal to \( r(k) \). Candidate values for \( u(k) \), that is \( u(k, i) \), can be computed using (4) with \( y(k + i) = C_{\text{ref}}(k) \) yielding

\[ u_c(i, k) = \frac{C_{\text{ref}}(k)}{C_d A_d^{i-1} B_d} - \frac{C_d A_d^i}{C_d A_d^{i-1} B_d} x(k). \]

It can be demonstrated that the \( u(k) \) is given by

\[ u(k) = \min(u_c(i, k)) \quad \text{with} \quad 1 \leq i \leq N - 1, \]

and \( N \) must be large enough such the time prediction interval includes the maximum value of the impulse response. This control law can be interpreted as being able to compute the minimum drug amount (bolus) at each time instant that provides the maximum desired effect, as such, it is named min–max TCI. Figure 7 shows results obtained with a computer simulation to evaluate the control algorithm defined by (4)–(6), and using the Schnider model, parameterized for a 60 year male patient, with 90 kg and 175 cm of height. The reference signal evolves according to a square wave. The output and the state variables are shown at the top and the control signal is shown at the bottom. The control law was parameterized by \( C_d = [0.03 \, 0.0 \, 0.97] \) that corresponds to control an output that includes the concentration at the central compartment and at the effect-site.

**FIGURE 7**  Control of the Schnider model using the virtual output \( y(k) = [0.03; \, 0; \, 0.97] x(k) \) that includes the drug concentration at the central compartment. (In upper plot: effect concentration in solid line, plasma concentration in dashed line, reference in dotted line and peripheral compartment concentrations in dot-dashed line)
Based on the computer simulation, the duration of the transient caused by the reference on drug concentration at the effect compartment is found to be 1.5 min for a positive step and 2.5 min for a negative step.

5.2 Closed-loop TCI for DoA/BIS index

From the results described previously with the predictive min–max TCI and the Schinder model, it is possible to change the effect concentration to a new steady state value in 2.5 min. The relation between the drug concentration at the effect compartment and the observed effect $E$, measured by the BIS index, is usually described by the static Hill function. In the case of the DoA/BIS, the Hill function may include more than one drug, being used in this case to describe the synergy between a hypnotic drug propofol and an analgesic drug such as remifentanil at the effect side.

The concentration-response is approximated by (7)

$$E = E_0 + \left( E_{max}(\theta) - E_0 \right) \frac{U_a + U_b}{U_a + U_b + U \theta} \frac{\gamma(\theta)}{1 + \left( \frac{U_a + U_b}{U \theta} \right)^{\gamma(\theta)}},$$

(7)

where $U_a = \frac{[A]}{C_{a,s}}$, $U_b = \frac{[B]}{C_{a,s}}$, $\theta = \frac{U}{U_a + U_b}$, where $[A]$ and $[B]$ represents the concentration of the anesthetic drugs (A, B), and $C_{a,s}$ is the concentration associated with 50% drug effect and $\gamma(\theta)$ determines the steepness of the response which is a function of $\theta$. A compact representation of the function (7) is given by by $BIS[k] = f_{\text{H}}(C_p[k], C_r[k])$, where $C_p$ and $C_r$ represent the effect site concentration of propofol and remifentanil.

Considering that 2.5 min after a step on the TCI reference the drug concentration at the effect site $C_e[k]$ reaches the steady state, one assumes even if there is dynamic uncertainty, that $C_e$ will reach the steady state value in the same time interval. By sampling $C_e$ synchronously with the changes of the TCI reference and with a sampling time larger than 2.5 min, an iterative procedure can be used, based on $BIS[k] = f_{\text{H}}(C_p[k], C_r[k])$, to adjust the reference of the TCI controller.

A linearization of the Hill function can be written as

$$BIS[k] = BIS_{ref} + k_p(C_e[k] - C_{\text{ref}}) + \Delta,$$

(8)

where $BIS_{ref}$ is the BIS reference, $C_{\text{ref}}$ is the propofol effect concentration reference, $k_p$ is the local derivative that is negative (an increase in the $C_e$ corresponds to a decrease in the BIS index) and $\Delta$ represents higher order terms as well the effect of other drugs such as the remifentanil.

By rearranging the terms of (8) and considering that, there is uncertainty in the steady state value of $C_e$, computed from the Schnider model ($\hat{C}_e$), the reference signal for the drug concentration effect is written as

$$C_{\text{ref}} = \hat{C}_e[k] + \frac{1}{k_p} (BIS_{\text{ref}} - BIS[k]) + \Delta.$$

(9)

This equation motivates the use of integral control to increase/decrease the reference of drug concentration at the effect site, whenever, $BIS[k]$ is above/below $BIS_{ref}$, 

$$C_{\text{pref}}[k + 1] = C_{\text{pref}}[k] + \frac{1}{k_p} (BIS_{\text{ref}} - BIS[k]),$$

(10)

where $(BIS_{\text{ref}} - BIS[k])$ is the BIS tracking error and $k_p$ is a gain that is adjusted either online (adjustable knob) or based on model identification using previous data ($0 > k_p [k] > 20$). The procedure used to estimate $k_p$ involves two steps: (a) Configuration of the Schnider model with patient data; (b) Identification of the relation between the drug concentration at effect site and the BIS level, which is assumed that is a static function.

It must be emphasized that the closed-loop min–max TCI is composed by an integral component, described by (10), and by the predictive control law (5) that computes the infusion rate. The integral component is used to close the control
loop, it uses the BIS tracking error to adjust the reference of drug concentration at the effect site in the predictive control law (5).

5.3 Neuromuscular blockade control

As an example to control NMB, a PID controller was implemented based on the basic PID representation\(^5\) and the one proposed in Reference 4 with the mechanism of automatic detection of spontaneous recuperation, the OnLine tuned algorithm for recovery detection.\(^6\) This controller uses the NMB behavior induced for the initial bolus to tune the PID parameters and begins the controlled infusion when the spontaneous recuperation of NMB starts. In general anesthesia, during the induction phase, the patient receives a high dose of muscle relaxant with the initial bolus that causes a fast drop in the value of NMB that may reach 0%, corresponding to total neuromuscular blockade. After the end of the anesthesia induction phase it is very likely that the patient stays in a state of total neuromuscular blockade during 15–45 min approximately. After this time, the patient begins the spontaneous recuperation, that may be automatically detected by OnLine tuned algorithm for recovery detection.\(^6\)

The equations that define the discrete-time PID controller are

\[
U_d[k] = K_c e[k] + K_v \frac{e[k]}{T_s} + \text{INT}_e[k],
\]

\[e[k] = \text{NMB}[k] - \text{NMB}_{\text{ref}}[k]
\]

with

\[
\text{INT}_e[k + 1] = \text{INT}_e[k] + \frac{K_c}{\tau_i} e[k],
\]

where:
- \(U_d[k]\): the control variable (rocuronium infusion rate) \(\text{NMB}[k]\): is the neuromuscular blockade value in % \(\text{NMB}_{\text{ref}}[k]\): is the neuromuscular reference in % \(e[k]\): is the error between neuromuscular blockade value \(\text{NMB}[k]\) and desired reference \(\text{NMB}_{\text{ref}}[k]\) \(K_c\): is the proportional gain \(\tau_i, \tau_d\): are the integral time and derivative time constants \(\text{INT}_e\): denotes the integral of error and \(T_s\): is the sampling interval.

The controller parameters \((K_c, \tau_i, \text{and } \tau_d)\) are obtained by the method described in Reference 37, using

\[
K_c = \frac{1.2}{L \cdot R} \cdot \frac{1}{\text{rd}(\eta_0)} \text{µgkg}^{-1}\text{min}^{-1}
\]

\[
\tau_i = 2 \cdot L \text{ min } \tau_d = L \cdot 2 \text{ min}
\]

\[
\text{rd}(\eta_0) = \left. \frac{\partial r(t)}{\partial C_r(t)} \right|_{t = \eta_0}
\]

\[
\text{rd}(\eta_0) = \frac{\text{NMB}_{\text{ref}} \cdot S(\frac{100}{\text{NMB}_{\text{ref}}})^{1-1/S}}{100C_{50}},
\]

where \(L\) and \(R\) are deduced form the Ziegler–Nichols step response method, applied to the linear part of the combined pharmacokinetic/pharmacodynamic model, and \(\text{rd}(\eta_0)\) is the partial derivative evaluated at the target value \(\eta_0\).\(^8\) The tuning method uses the time interval value computed from the administration of the first bolus to the time instant where the NMB reaches 50% referred, as \(T_{90}\). Next, a database with a set of 100 previously identified \((L, R)\) parameters for atracurium\(^9\) is searched to find a case with a \(T_{90}\) closest to the actual value, and the corresponding parameters \((L, R, S, C_{50})\) are used to compute \(K_c, \tau_i, \text{and } \tau_d\) to (12). In a case where a different drug of the atracurium family is used, an assumed clinical factor power \((F_{\text{pow}})\) is applied to scale the drug amount to relate its potency to the potency of atracurium. As an example: for rocuronium \(F_{\text{pow}} = 1.2\), and for cisatracurium \(F_{\text{pow}} = 0.3\).
5.4 Platform and control performance

The closed-loop predictive min–max TCI for BIS index, described in Sections 5.1 and 5.2, was tested using the GALENO platform in 10 clinical cases. In all the cases the controller used the induction phase data (BIS and steady-state effect concentration given by the Schnider model) to tune the controller, that is started after the induction phase, with the BIS index stabilized around 50. During the induction phase, due to clinical restrictions, the administration of induction bolus was performed by the anesthesiologist using the platform. The moment to close the control loop is an anesthesiologist’s decision based on his assessment of the situation.

Figures 8 and 9 show the control results which are representative for the tested cases. In the first case the duration of the anesthesia is 100 min and in the second case the duration is 500 min. The reference for the BIS is manipulated by the anesthesiologist. The BIS tracking error was kept in the clinical desired values. Other clinical cases are shown in Figure 10.

**Figure 8** Effect site concentration target, infusion rate of propofol, and BIS tracking for a real clinical case. During the controlled infusion period, the BIS error was ±10

**Figure 9** Effect site concentration target, infusion rate of propofol, and BIS tracking for a real clinical case. During the controlled infusion period, the BIS error was less ±10
**Figure 10** Performance of closed-loop predictive min–max TCI controller for DoA/BIS in 12 case studies in clinical setting. BIS index is in solid line, reference in dashed line, and the start of controlled infusion is marked with a diamond shape.

**Figure 11** Neuromuscular blockade tracking and infusion rate of rocuronium. During the controlled infusion period the reference was perfectly tracked. At minute 90, the reference was altered to 5%, but the controller shows adequate tracking of the new reference.

The PID controller for NMB described in Section 5.3 was used in 20 clinical cases, and all of them the NMB was kept near the target. Figure 11 illustrates the result of a case where the blocking agent rocuronium was used. The autotuning of the controller parameters was adequate to handle the patient’s characteristics and dynamics.

References 9–14 present experimental results based on other control methodologies.

6 | CONCLUSION

The GALENO platform is a software application for monitoring, modeling and control of anesthesia that has been developed under the GALENO project. It has been successfully applied and validated in more than 350 surgeries with general...
anesthesia at the surgery rooms of the two Hospital Centers using several closed-loop control algorithms. In the test phase, the GALENO platform proved to be an adequate clinical software, which integrates a wide range of functionalities, being the product of the cooperation with the team of anesthesiologists involved in the project: "Hospital Santo António- Centro Hospitalar do Porto" and "Hospital Pedro Hispano- Unidade Local de Saúde de Matosinhos". All the functionalities are supported in two operation modes: (i) off-line mode to perform data analysis and modeling identification, database processing and advanced simulation for modeling and control of DoA/BIS and NMB with training purposes and (ii) real-time mode to automatically perform TIVA in general anesthesia procedure including the induction and control of DoA/BIS and NMB in maintenance phase. A quite relevant feature is its expansibility that allows the development and inclusion of new communication modules to work with other medical equipments (infusion pumps, and biomedical monitors), new control and filtering algorithms. Presently 13 control algorithms for DoA/BIS index and NMB Index are implemented and are available in the GALENO platform. The GALENO software platform was used in real cases with duration up to 8 h of continuous operation. The conclusion is that it fulfills the design requirements for rapid prototyping and testing of new control algorithms in a clinical setting, with performance level that satisfies clinical criteria.

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CONFLICT OF INTEREST
No conflict of interest.

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