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ORIGINAL RESEARCH

An enriched simulation environment for evaluation of closed-loop anesthesia

Mengqi Fang · Yuan Tao · Youqing Wang

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Abstract To simulate and evaluate the administration of anesthetic agents in the clinical setting, many pharmacology models have been proposed and validated, which play important roles for *in silico* testing of closed-loop control methods. However, to the authors' best knowledge, there is no anesthesia simulator incorporating closed-loop feedback control of anesthetic agent administration freely available and accessible to the public. Consequently, many necessary but time consuming procedures, such as selecting models from the available literatures and establishing new simulator algorithms, will be repeated by different researchers who intend to explore a novel control algorithm for closed-loop anesthesia. To address this issue, an enriched anesthesia simulator was devised in our laboratory and made freely available to the anesthesia community. This simulator was built by using MATLAB® (The MathWorks, Natick, MA). The GUI technology embedded in MATLAB was chosen as the tool to develop a human–machine interface. This simulator includes four types of anesthetic models, and all have been wildly used in closed-loop anesthesia studies. For each type of model, 24 virtual patients were created with significant diversity. In addition, the platform also provides a model identification module and a control method library. For the model identification module, the least square method and particle swarm optimization were presented. In the control method library, a proportional-integral-derivative control and a model predictive control were provided. Both the model identification module and the control method library are extensive and readily accessible for users to add user-defined functions. This simulator could be a benchmark-testing platform for closed-loop control of anesthesia, which is of great value and has significant development potential. For convenience, this simulator is termed as Wang's Simulator, which can be downloaded from http://www.AutomMed.org.

Keywords Closed-loop anesthesia · Simulator · Pharmacology model · Proportional-integral-derivative control · Model predictive control

1 Introduction

With the rapid development of medical science, more and more surgical procedures are being performed. In order to ensure patient safety, quality of care, cost-containment and a quiet, stress-free working environment, anesthetic techniques are evolving. Traditional anesthetic administration involves anesthetists dispensing volatile and intravenous agents without feedback loops incorporated into their apparatus to control anesthetic drug administration. In other words, anesthetists regulate the amount of anesthetic agent delivered to their patients according to their interpretation of their patients' physiologic status. Despite the skill and experience of even the most astute clinicians, over dosage and under dosage can occur. This can lead to major potential postoperative complications such as cardiovascular and neurologic events in the case of anesthetic overdose and awareness during anesthesia with under dosage. To deal with this issue and lessen the possibility of error in drug dosages and administration, researchers have

Declaration: The experiments comply with the current laws of the country in which they were performed.

M. Fang · Y. Tao · Y. Wang (✉)
College of Information Science and Technology, Beijing University of Chemical Technology, Mail Box 4, 15# Beisanhuan East Road, Beijing 100029, China
e-mail: wang.youqing@ieee.org

incorporated automatic control technology into devices for clinical anesthetic administration, utilizing the concept of closed-loop anesthesia. It has been demonstrated that closed-loop control of anesthesia is feasible and as good as or even better than human delivery relative to control of drug concentrations and dosages [1, 2].

The depth of anesthesia during an operation can be measured utilizing three indices, i.e. hypnosis, analgesia, and neuromuscular blocking (NMB) degree. These indices should be controlled simultaneously relative to their respective proper levels during anesthetic administration. The level of hypnosis can be assessed by analyzing the electroencephalogram, such as median frequency, spectral edge frequency, bispectral index, wavelet-based anesthetic value for central nervous system, anesthesia entropy, and so on [3–5]. Among those hypnosis monitoring indices, BIS is the earliest one available for commercial application approved by the US Food and Drug Administration and it also appears to be one of the most promising indices to monitor hypnosis level [6, 7]. The estimation of patients' antinociception can be reflected by the electroencephalogram as well as heart rate variability [3]. For NMB monitoring, the patients' reactions to nerve stimulation can be used to evaluate the extent of block. However, several issues relating to ongoing control of the extent of neuromuscular block by servo mechanisms, such as the determination of the set point have not yet been resolved. Nonetheless, NMB is still the most evolved of closed-loop control technologies relating to anesthetic agent administration, due to the well developed monitoring devices and less innate complexity of the feedback monitoring system.

To design closed-loop anesthesia, the physiological and pharmacological parameters of patients should be well understood and individualized models should be constructed. There are a number of available methods to build pharmacokinetics-pharmacodynamics (PK-PD) models. Among these methods, compartmental modeling method [8, 9] is widely used due to its simplicity and effectiveness. However, when modeling the pharmacokinetic and pharmacodynamics patterns of various anesthetics, one must take into account that they differ with respect to one another as well as to various types of patients. Hence, when modeling various virtual patients, the drugs used in this simulator should first be decided upon and then the corresponding models should be selected, evaluated and incorporated into the simulation algorithms in accordance with the fixed drugs. Accordingly, four classes of anesthetic drugs were selected for use in the simulation scenarios. For hypnosis, the intravenous drug propofol and the inhalational drug isoflurane were chosen because they are widely utilized as components of general anesthesia. In terms of analgesia and NMB, remifentanil, a rapidly acting intravenous narcotic and atracurium, a widely used NMB agent were chosen for their high appearance frequency in the relevant references, a reflection of their popularity among anesthetists.

Hypnotic intravenous agent model selection: Propofol is one of the mainstream intravenous drugs, widely used for induction of general anesthesia throughout the world. During the past two decades, a large number of researchers have concentrated on the exploration of PK-PD models of propofol. As a result, there are many propofol pharmacology models describing the uptake and elimination of this drug in patients during surgical anesthesia [10–16]. After evaluation and comparison, it is concluded that the models developed by Marsh et al. [16], Schnider et al. [10] and Schüttler et al. [12]. have been adopted by many researchers, due to their simplicity and wide range of individuality. However, according to the experimental result derived by Masui et al. [17], the Schnider propofol model was finally incorporated into this platform as it appeared to be more appropriate for use in Target Controlled Infusion systems and advisory displays systems than the other two models.

Hypnotic inhalational agent model selection: For modeling the behavior of isoflurane on closed-loop anesthesia delivery systems, the isoflurane models developed by Frei et al. [18], Yasuda et al. [19] and Schnider et al. [20] were chosen and incorporated into this platform.

Opioid agent model selection: For modeling opioid behavior, several models for opioid are proposed by various research groups [21–23]. Remifentanil, a typical opioid drug, was selected for use in the simulator, and the corresponding model presented by Minto et al. [24] was utilized.

Neuromuscular blocking (NMB) agent model selection: Because NMB technology has been well developed and administration of NMB degree is easier to control and monitor in closed-loop systems than is the case for hypnotics and narcotic agents, there are few NMB models in commercially used Target Controlled Infusion and advisory display systems. The atracurium model proposed by Weatherley et al. [25] was used in the simulator. In summary, these four selected models for hypnosis, analgesia and NMB, enjoy wide acceptance in the anesthesia community, and are relatively simple and straightforward to incorporate into simulations. The following sections discuss our use of these models in greater detail.

Up to now, various kinds of control strategies for closed-loop administration of anesthetic agents have been developed and validated. Some of these studies focused upon simulating real-world anesthesia procedures utilizing sophisticated control algorithms. For example, Dumont et al. [26] have conducted a robust hypnosis control system involving simulation; two predictive control algorithms proposed by Niño et al. [27] and Ionescu et al. [28] have been simulated on virtual patients to test the performance of hypnosis control systems; a feedforward adaptive control system was raised by Nunes et al.

[29] and realized in silico to regulate propofol dosing; and a simulation comparison of four hypnosis closed-loop control algorithms has been proposed by Yelneedi et al. [30]. Apart from the simulation studies, some closed-loop anesthetic algorithms have been developed and validated in clinical studies by a large number of researchers. For example, the proportional-differential and proportional-integral-derivative (PID) control algorithms were used by Liu et al. [2, 31] to design the delivery strategy for propofol; another kind of robust system was raised by Mendonça et al. [32] for the control of NMB level; a novel rule-based adaptive closed-loop control system was raised by Hemmerling et al. [33] for propofol administration; and a model predictive control system designed by Furutani et al. [34] and PID control systems designed by Liu et al. [5, 35] were adopted to control a combined hypnosis and analgesia system. From the perspective of control theory, all of these applied closed-loop control methods can be roughly divided into three categories: (1) typical traditional feedback control; (2) intelligent control and (3) model-based advanced control. Accordingly, PID controller, fuzzy logic controller, and model predictive control are frequently used in closed-loop anesthesia [36]. Although the studies based on intelligent control and model-based control were widely employed over the past several decades, traditional controller technology, e.g. the PID controller, still played a dominant role in the clinical setting.

When researchers want to test a new closed-loop control algorithm *in silico*, they have to select a proper model of virtual subject in advance. However, since there are so many PK-PD models available, the researchers must spend considerable time and effort consulting and assessing related articles in order to find and select the models most appropriate for their needs. In order to save the researchers' time, we constructed a library of widely used virtual subject models after investigating and collecting numbers of reported patient models. Finally, we combined the model database and the control algorithm database into an anesthesia simulation platform to imitate the practical anesthesia situation. This newly proposed simulation platform which was built by using MATLAB® (The MathWorks, Natick, MA) [37] is mainly designed for researchers to test new closed-loop control algorithms, and it also has the following advantages. First, the platform can save the time of finding and simulating appropriate virtual subject models for researchers, especially for novices. Second, this platform has collected several anesthesia models with a wide range of usage, so it can also act as an information bank for anesthesia with great reference value. Third, with this simulation platform, once researchers come up with a novel control method, they can test this new method's stability and security before doing clinical trials. In addition, different from clinical experiments, this platform can provide a relatively fair and stable situation, which is convenient for researchers to compare different advanced control methods. Last but not least, this platform is extendible, which means users can freely expand model and control method libraries if needed.

Our simulation platform mainly involves two integrated libraries, the virtual subject library and the control method library. The former one aims to provide virtual patients and the latter one is convenient for researchers to develop new control algorithms for closed-loop anesthesia. The virtual subject library consists of four published anesthetic models [10, 11, 18–20, 24, 25], upon which 24 virtual patients were generated with significant diversity. In the control method library, four control modes and two closed-loop control strategies were provided as benchmark programs. In addition, this division also includes complete extendible ports. In our simulator, some other functions, such as model identification, noise simulation, and so on, are also involved for researchers' convenience.

The rest part of this paper is organized as follows. The specific structures, functions, development process, and expansion methods of this simulation platform are presented in Sect. 2. In Sect. 3, a simple PID control algorithm is adopted to illustrate how to use this platform to develop and test a new control algorithm. In Sect. 4, some conclusions of this study are provided; in addition, some drawbacks and some potential solutions of the present simulation platform are discussed and suggested for the future study.

2 Establishment of the simulator

2.1 Platform specific structures

The overall structure of the anesthesia simulator that we constructed is shown in Fig. 1. As can be seen from Fig. 1, this platform consists of three fundamental modules: (1) virtual patient division; (2) model identification division and (3) control algorithm division. Each division has its own specific functions and supports certain appropriate expansions for the users' convenience, and the combinations of these divisions enable additional configurations for users' specialized research needs and applications. In the following sections, the specific structures, rough functions, brief methodology of developing and expanding the simulator are introduced for each division. Finally, the interactions of the three components are summarized.

2.2 Model library development and virtual patient generation

2.2.1 The model library

Considering the major purpose of establishing this simulator, the virtual patient division can be treated as the

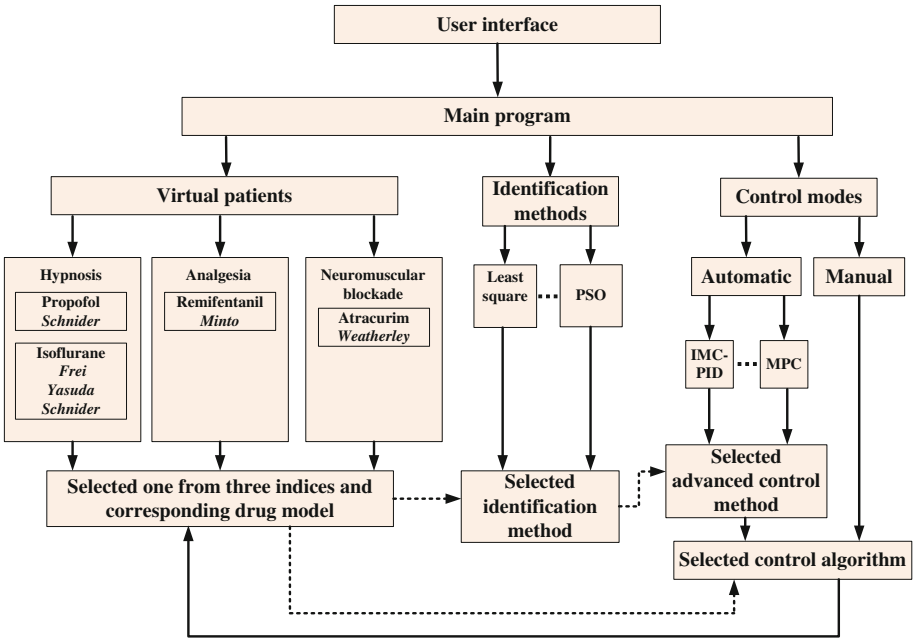

Fig. 1 The integral structure of anesthesia simulator. The models proposed by Schnider et al. [10, 11, 20], Frei et al. [18], Yasuda et al. [19], Minto et al. [24], and Weatherley et al. [25] have been listed in this figure and abbreviations PSO, IMC-PID and MPC denote Particle Swarm Optimization, Internal Model Control-Proportion Integration Differentiation, and Model Predictive Control, respectively. The dashed line was used for the arrow from "selected one from three indices and corresponding drug model" to "selected control algorithm", because this arrow exists only when the closed-loop control method is used. The dashed lines were also used for the arrows around "selected identification method", because the model identification block is flexible and could be chosen to activate or not according to the users' needs

kernel of this platform. As mentioned in the introduction, this platform includes four kinds of drug models, and the detailed drug models are introduced in the subsequent contents.

2.2.1.1 Propofol The propofol PK-PD model developed by Schnider et al. [10, 11] can be treated as a combination of two separated parts—the PK and PD parts. The PK part has a three-compartmental structure which can be modeled by third-order linear differential equations based on the mass balance theory, while the PD part is modeled by a first-order differential equation and Hill equation which can be treated as a static nonlinear term. Hence, the total Schnider propofol model can be treated as a wiener system, and its integral formulation is presented as follows.

The PK model can be described as the following linear differential equations.

$$\begin{aligned}\frac{dC_1(t)}{dt} &= -(k_{10}+k_{12}+k_{13})C_1(t)+k_{21}\frac{V_2}{V_1}C_2(t)\\ &\quad +k_{31}\frac{V_3}{V_1}C_3(t)+\frac{1}{V_1}u(t)\\ \frac{dC_2(t)}{dt} &= k_{12}\frac{V_1}{V_2}C_1(t)-k_{21}C_2(t)\\ \frac{dC_3(t)}{dt} &= k_{13}\frac{V_1}{V_3}C_1(t)-k_{31}C_3(t)\end{aligned} \tag{1}$$

where C_1, C_2 and C_3 denote the concentration of drug in the central compartment and the other two peripheral compartments, respectively. The constants V_i (i = 1, 2, 3) denote the volume of the *i*th compartment, and the constants k_{ij} (i, j = 1, 2, 3, i ≠ j) represent the drug amount transfer rate from the *i*th compartment to the *j*th compartment. The constant k_{10} represents the drug metabolism rate, and u (t) is the infusion rate of propofol. In the Schnider propofol model, some personalized parameters are shown in Table 1 [28].

In Table 1, lean body mass (lbm) is related with the patient's gender. Parameters C_{l1}, C_{l2}, and C_{l3} denote the clearance rates of the corresponding compartments, and the transfer and metabolism rates should be calculated according to the clearance rates as denoted in Eq. (2).

$$k_{10}=\frac{C_{l1}}{V_1},\ k_{12}=\frac{C_{l2}}{V_1},\ k_{13}=\frac{C_{l3}}{V_1},\ k_{21}=\frac{C_{l2}}{V_2},\ k_{31}=\frac{C_{l3}}{V_3} \tag{2}$$

From the above formulas, a conclusion that the age (in year), weight (in kilogram), height (in centimeter) and gender of a patient decide the PK model can be derived. The PD model, a first-order differential term and a nonlinear Hill equation, which aims to combine the drug concentration with the drug effect, is presented in Eq. (3).

Table 1 The PK parameters of the Schnider propofol model, where "lbm" represents the lean body mass

PK parameters	Values or computational formulas
V_1 [1]	4.27
V_2 [1]	18.9 − 0.391 (age − 53)
V_3 [1]	238
C_{l1} [1/min]	1.89 + 0.0456 (weight − 77) −0.0681 (lbm − 59) + 0.0264 (height − 177)
C_{l2} [1/min]	1.29 − 0.024 (age − 53)
C_{l3} [1/min]	0.836
lbm (for male)	$1.1\text{weight} - 128\frac{\text{weight}^2}{\text{height}^2}$
lbm (for female)	$1.07\text{weight} - 148\frac{\text{weight}^2}{\text{height}^2}$

$$\begin{aligned} \frac{dC_e(t)}{dt} &= k_{e0}(C_1(t) - C_e(t)) \\ BIS(t) &= E_0 - E_{\max}\frac{C_e^{\gamma}(t)}{C_e^{\gamma}(t) + EC_{50}^{\gamma}} \end{aligned} \tag{3}$$

where C_e denotes the drug concentration of the effect compartment, an imaginary compartment. The constant k_{e0} reflects the transfer ratio between the central compartment and the effect compartment. E_0 and E_{max} denote the baseline and maximum effect value of BIS, respectively, and are typically assigned a value of 100. EC_{50} is the drug concentration at half maximal effect and γ determines the steepness of the curve in Hill equation.

In the Schnider propofol PK-PD model, the parameters age, weight, height, EC_{50}, γ, and the patient's gender can reflect the patient's individuality and are also the cues of creating virtual patients.

2.2.1.2 Isoflurane The isoflurane model can be divided into three parts—the simplified respiratory system model proposed by Frei et al. [18], the five-compartmental PK model proposed by Yasuda et al. [19] and the PD model proposed by Schnider et al. [20]. During the simulation process, the reference of Gentilini et al. [38] was referred to detail this model. Because isoflurane is a volatile inhaled anesthetic agent, the patient's respiratory system model should be incorporated into the model. For the sake of modeling convenience, the originally complex respiratory system model is reduced to a first-order function which has relative accuracy and is described as following [18].

$$\begin{aligned} V\frac{dC_{insp}}{dt} &= Q_0C_0 - (Q_0 - \Delta Q)C_{insp} \\ &\quad - f_R(V_T - \Delta)(C_{insp} - C_1) \end{aligned} \tag{4}$$

where V is the volume of the respiratory system; C_1 denotes the alveolar concentration; f_R is the respiratory frequency; V_T represents the tidal volume; Δ is the physiological dead space; ΔQ denotes the losses of the breathing circuit through the pressure-relief valves; Q_0 and C_0 are the fresh gas flow and its anesthetic concentration entering the respiratory circuit, respectively. The unit of V, V_T, and Δ is liter; the unit of C_0, C_1, and C_{insp} is percent; the unit of Q_0 and ΔQ is liter per minute. Among these variables, C_0 is the manipulated variable which is also the input variable of this model, and C_{insp} is the output variable.

The five-compartmental PK model of isoflurane, which can be treated as fifth-order differential equations, is represented in Eq. (5).

$$\begin{aligned} \frac{dC_1}{dt} &= \sum_{j=2}^{5}\left(k_{j1}C_j\frac{V_j}{V_1} - k_{1j}C_1\right) + \frac{f_R(V_T - \Delta)}{V_1}(C_{insp} - C_1) \\ \frac{dC_2}{dt} &= k_{12}C_1\frac{V_1}{V_2} - k_{21}C_2 - k_{20}C_2 \\ \frac{dC_j}{dt} &= k_{1j}C_1\frac{V_1}{V_j} - k_{j1}C_j \quad (j = 3,4,5) \end{aligned} \tag{5}$$

where the constants V_i (i = 1, …, 5) denote the volume of the *i*th compartment, and the constants C_i (i = 2, …, 5) denote the drug's concentration in the *i*th compartment. Similar to the abovementioned propofol three-compartmental model, the constants k_{ij} (i, j = 1, …, 5, i ≠ j) represent the transfer rate of isoflurane from the *i*th compartment to the *j*th compartment. The constant k_{20} represents the drug metabolism rate. In the isoflurane PK model, the parameters V_i (i = 1, …, 5), k_{ij} (i, j = 1, …, 5, i ≠ j) and k_{20} vary with various patients.

The structure of isoflurane PD model is the same as Eq. (3) and the main differences are the numerical values of constants k_{e0}, EC_{50} and γ. Hence, in the whole isoflurane model, the parameters V_i (i = 1, …, 5), k_{ij} (i, j = 1, …, 5, i ≠ j), k_{20}, k_{e0}, EC_{50} and γ can be changed to create various virtual patients.

2.2.1.3 Remifentanil The remifentanil PK-PD model developed by Minto et al. [24] is the combination of a three-compartmental PK model and a PD model constructed by a first-order function plus a static nonlinear term called Hill equation. So the structure of the referred remifentanil model is similar to the Schnider propofol model, and the main differences appear in the calculations of parameters and the controlled index. The remifentanil PK model has a structure described in Eq. (1), and the relevant parameters are represented in Table 2 [38].

In Table 2, lbm also represents the lean body mass, and the transfer rates k_{10}, k_{12}, k_{13}, k_{21}, k_{31} can also be calculated according to Eq. (2). Therefore, the remifentanil PK

Table 2 The PK parameters of the Minto remifentanil model

PK parameters	Computational formulas and values
V_1 [1]	5.1 − 0.0201 (age − 40) + 0.072 (lbm − 55)
V_2 [1]	9.82 − 0.0811 (age − 40) + 0.108 (lbm − 55)
V_3 [1]	5.42
C_{l1} [1/min]	2.6 − 0.0162 (age − 40) + 0.0191 (lbm − 55)
C_{l2} [1/min]	2.05 − 0.0301 (age − 40)
C_{l3} [1/min]	0.076 − 0.00113 (age − 40)

model can be determined after the determination of patient's age, height, weight and gender. And then the remifentanil PD model is represented as below.

$$\begin{aligned} \frac{dC_e(t)}{dt} &= k_{e0}(C_1(t) - C_e(t)) \\ SEF(t) &= SEF_0 + (SEF_{MAX} - SEF_0)\frac{C_e^{\gamma}(t)}{C_e^{\gamma}(t) + EC_{50}^{\gamma}} \end{aligned} \tag{6}$$

where k_{e0} and EC_{50} under the half maximal effect condition are related to the patient's age, the baseline value $SEF_0 = 20$, and the maximal effect value $SEF_{MAX} = 5.5$. Finally, in the complete remifentanil model, the parameters age, weight, height, and even gender can be the personalized parameters which can be changed properly to generate different virtual individuals.

2.2.1.4 Atracurium The atracurium PK-PD model developed by Weatherley et al. [25] can be treated as a two-compartmental PK model and a PD model including a second-order function and nonlinear Hill equation in series. In order to confirm and detail this model, another Ref. [39] is referred. The atracurium PK model is shown in the following equations.

$$\begin{aligned} \frac{dx_1(t)}{dt} &= -\lambda_1 x_1(t) + a_1 u(t) \\ \frac{dx_2(t)}{dt} &= -\lambda_2 x_2(t) + a_2 u(t) \\ C_p(t) &= x_1(t) + x_2(t) \end{aligned} \tag{7}$$

where x_i (i = 1, 2) denotes the state variables and a_1, a_2 (in kilograms per mililiter), λ_1, λ_2 (in per minute) are the patient-dependent parameters. The drug infusion rate u (t) (in micrograms per kilogram per minute) is the input of this PK model, and the plasma concentration C_p (t) (in micrograms per milliliter) is the output of this PK model.

The atracurium PD model is described as a cascade of a second-order function and a nonlinear term, and it is formulated as following.

$$\begin{aligned} \frac{dC(t)}{dt} &= -\lambda C(t) + \lambda C_p(t) \\ \frac{dC_e(t)}{dt} &= -\frac{1}{\tau}C_e(t) + \frac{1}{\tau}C(t) \\ r(t) &= \frac{100EC_{50}^{\gamma}}{EC_{50}^{\gamma} + C_e^{\gamma}(t)} \end{aligned} \tag{8}$$

where C_e (t) is the drug concentration of the effect compartment, C (t) is an intermediate variable, and r (t) (in percent) is the reflection of NMB level. And γ (in per minute), τ (in minutes), EC_{50} (in micrograms per milliliter) and γ (dimensionless) are patient-independent parameters. Finally, in the whole atracurium PK-PD model, the parameters a_i (i = 1, 2), λ_i = 1, 2, λ, τ, EC_{50}, λ are the patient-dependent parameters and also the cues to generate virtual patients.

Once the individual parameters are selected, the abovementioned four drug models can be used to reflect the designate patient's overall anesthesia situation. Users could choose to control one from three indices by selecting the proper model, and all the models are all single input single output models.

2.2.2 *The development and expansion of model library*

2.2.2.1 Model library development By examining the four drug models described in Sect. 2.2.1, it can be inferred that all of the models could be treated as a cascade of a linear system denoted by differential equations and a nonlinear system denoted by the Hill equation. Accordingly, the core of model realization in the platform is to solve the underlying differential equations, and all the related programs serve this single aim.

In this platform, the Runge–Kutta iteration algorithm was used to solve the differential equations numerically by using the command "ode45" in MATLAB. Before solving equations, the model parameters should be given, and the time span used during solution process should be settled according to sampling time for convenience of simulating discrete control in practice. After solving the differential equations, the numerical value of the effect compartment concentration C_e would be extracted to calculate the corresponding anesthesia index according to the PD model. In conclusion, the procedures of model library development consist of the following steps: (1) setting relevant model parameters; (2) solving the differential equations and (3) calculating the final anesthesia index. The steps are then packaged into an m-file called "VIRTUAL_SUBJECT.m" in this platform.

The "VIRTUAL_SUBJECT.m" file can be regarded as a virtual patient under anesthesia, and it can also be treated as a black-box model whose inputs are the drug infusion

rate and the parameters, and outputs are effect compartment concentration and anesthesia index, i.e. hypnosis, analgesia, and NMB index. By accessing the abundant ports provided, users can choose and manipulate controlled variables freely, add confounding factors to simulate actual clinical situations encountered in the operating room and also extract intermediate but useful variables according to their needs.

2.2.2.2 Model library expansion The main function of the model library division is to provide an object and generate some meaningful data for users to test the performance of control or identification algorithms, diagnose the potential faults and even train the novice, e.g. anesthesia residents, etc. In addition, another advantageous feature of this division is its relatively simple extensible function. To enrich the model library, users could choose to add other models, and the following steps are provided as a reference.

Step 1: Add the requisite parameters of the added model, while taking care not to confuse them with the original data in the platform.
Step 2: Program to realize more models, and the existing models in the platform may be referred to or utilized as a sample or template.
Step 3: Add the symbol name of the additional model into the platform for convenience of choice.

While modifying parameters or adding models, it is important to pay close attention to the program's integrity and the uniqueness of program arguments to avoid confusion or programming errors.

2.2.3 Virtual patients generation

To establish a diversified simulation environment, this simulation platform provides 24 virtual patients (12 males and 12 females). First, one nominal male patient (M_adult#nominal) and one nominal female patient (F_adult#nominal) were created by using parameters from some related references [3, 10, 18, 19, 24, 28, 38, 39]. Taking the two nominal patients as the mean values, 20 of the remaining 22 patients (F_adult#001–M_adult#020) are generated using lognormal distribution method. Finally, the last two patients (M_adult#average, F_adult#average) are generated by calculating arithmetic mean parameter values of the other male and female virtual patients, respectively. Obviously, the two nominal patients reflect the average levels of all patients. Users can select the appropriate model type and then choose one or more virtual patients as needed.

In the process of creating and programming the virtual patients, the most basic task is to select and set the model parameters in order to solve the equations. Once this is done, however, it is relatively simple to add additional virtual patients with differing physiologic profiles merely by choosing proper parameters and adding them into the platform. The detailed methodology and parameters are shown as following.

2.2.3.1 Lognormal distribution method The lognormal distribution method is a kind of algorithm to generate random numbers around certain mean value based on normal distribution approach. With the lognormal distribution method, if a series of random numbers denoted by x with mean value x_0 will be generated, the logarithm of $\frac{x}{x_0}$ which follows normal distribution should be generated first, and then the value of x can be derived. Specially, the logarithm of $\frac{x}{x_0}$ obeys normal distribution with zero mean and standard deviation σ. So the range of x can be changed by adjusting the σ value properly. The lognormal distribution method has the advantage that the generated random number x is still positive, which normal distribution approach cannot satisfy.

2.2.3.2 Virtual patients Considering the drug models described in Sect. 2.2.1, the personalized parameters are: (1) the patient's age, weight, height; (2) the compartmental volumes and transfer rates of the isoflurane PK-PD model; (3) the parameters a_i, λ_i ($i = 1, 2$), τ, λ of atracurium PK-PD model and (4) EC_{50}, γ of propofol, isoflurane and atracurium PD model. As the patient's gender merely decides the calculation of lbm rather than other parameters, the individual parameters of male and female nominal patients can be combined to illustrate in one table. After taking the nominal parameters as mean values and selecting suitable σ values, the personalized parameter ranges of other 20 patients can be settled. In summary, the personalized parameter values and ranges of the virtual patients are illustrated in the following Table 3.

2.3 Patient model identification division

2.3.1 Identification division introduction

Based on the virtual patient library, a patient model identification division is developed in this simulation platform. This division is an independent module, which can be used to identify the selected patient's model with various traditional or novel identification algorithms. On one hand, this division seems necessary because the patient's model usually cannot be achieved ahead of time during a surgical procedure. In this situation, model identification online or during anesthesia induction is essential, especially under the model-based closed-loop control condition, and a model identification division is set up in this platform in order to simulate this scenario. In addition, this model

Table 3 The personalized parameters of virtual patients in this platform

Personalized parameter		Nominal patient	F_adult#001–M_adult#020	M_adult#average	F_adult#average
Age		40	30–53	41	39
Weight		65	50.44–83.76	66.0870	64.4187
Height		165	153.99–176.8	164.2675	166.4503
Propofol	EC_{50}	7.5	4.106–13.698	7.8381	7.5418
	γ	3	1.65–5.45	3.1324	3.0223
Isoflurane	V_1	2.31	1.2018–4.44	2.4626	2.2377
	V_2	7.1	3.4527–4.6	7.4222	7.3193
	V_3	11.3	4.5441–28.1	12.6908	11.3889
	V_4	3	1.7647–5.1	2.9781	2.8675
	V_5	5.1	1.4948–17.4	6.3068	5.3432
	k_{12}	1.26	0.8481–1.872	1.2464	1.3804
	k_{13}	0.402	0.285–0.567	0.4108	0.3931
	k_{14}	0.243	0.1286–0.459	0.2324	0.274
	k_{15}	0.0646	0.0221–0.1888	0.0793	0.0737
	k_{20}	0.0093	0.0017–0.0504	0.0143	0.0097
	k_{21}	0.21	0.0967–0.456	0.1913	0.2557
	k_{31}	0.023	0.0076–0.0698	0.0274	0.0218
	k_{41}	0.003	0.0011–0.0081	0.003	0.0036
	k_{51}	0.0005	0.0002917–0.00857	0.00050066	0.00045504
	k_{e0}	0.3853	0.02477–5	0.8632	1.7508
	EC_{50}	0.7478	0.4959–1.094	0.8032	0.6673
	γ	1.534	0.7915–5	2.1795	1.4021
Atracurium	a_1	0.0305	0.016–0.0581	0.0317	0.0304
	a_2	0.0057	0.0039–0.0083	0.0055	0.006
	λ_1	0.395	0.24–0.65	0.406	0.4079
	λ_2	0.0375	0.0287–0.049	0.0374	0.0382
	λ	0.1055	0.0856–0.13	0.1044	0.1095
	τ	7.21	3.7134–13.999	7.9183	6.5723
	EC_{50}	0.655	0.5959–0.72	0.6534	0.6641
	γ	4.5	3.2661–6.2	4.4692	4.2350

identification division can also be used to test the performances of certain novel system identification algorithms. All the drug models in Sect. 2.2.1 can be considered as a type of system with linear differential terms and a static nonlinear term, which could be treated as a Weiner system. Hence, the model identification division could be used to test the performances of system identification algorithms aiming at a kind of special wiener system, and any other systems as an extension. On the other hand, if model identification is not necessary in the user's algorithm, this model identification division can be neglected directly by merely excluding the identified results out of the programmed algorithm.

2.3.2 *Identification division development*

In the circumstance of simulation, the existing model identification division is an independent function block with the identification algorithms programmed to deal with the input and output data generated from selected virtual patients. Considering the practical operation situation, the simulated drug infusion strategies provided in this platform are in two forms—constant infusion (i.e. step excitation signal) and bolus infusion (i.e. impulse excitation signal). There are also two model identification methods, least square method [40] and particle swarm optimization method [41, 42], in this platform. The least square method is a traditional system identification method which is based on the strict formula derivation. As a comparison, the particle swarm optimization method can be treated as a kind of intelligent search algorithm, and it may have a wider solution space than the traditional method dealing with certain special systems. The developing flow of model identification division is shown as following. First of all, the identification time, the virtual patients under identification, the form of input and the identification method

should be settled. Then the anesthesia scenario would be started by calling the function "VIRTUAL_SUBJECT.m" to generate the reaction data. At last, the collected reaction data would be processed to derive the model parameters of the selected virtual patients. All these procedures were packaged into an m-file called "model_identification.m" for the convenience of users to change or expand this division.

The two model identification algorithms embedded in this platform are represented as sample examples. In the two identification methods, the patient's model is formulated as a second-order difference equation denoted as Eq. (9).

$$a_2y(k-2)+a_1y(k-1)+a_0y(k)=b_1u(k-1) \tag{9}$$

where constants a_0, a_1, a_2, b_1 are the unknown model parameters. After introducing the backward lag operator q, the Eq. (9) can be rewritten in a transfer function form as Eq. (10). Finally, the numerator and denominator in Eq. (10) would be presented in the user interface as the model identification result, and the calculated parameters could be exported into the workspace for the usage of the model-based control algorithms if needed.

$$\frac{Y(k)}{U(k)}=\frac{b_1q^{-1}}{a_0+a_1q^{-1}+a_2q^{-2}} \tag{10}$$

2.3.3 Identification division expansion

From the above-mentioned introduction of this division, one conclusion that can be derived is that the current model identification is a type of open-loop and offline method. To expand this division, there are some alternative ways as follows.

1. On-line identification expansion: since this division is actually independent of the other components except virtual patient division in this platform, it could be embedded into the other programs reflecting the anesthesia process to act as a data processing program segment. The data collecting method should be adjusted accordingly, and the identification time period should also be considered.
2. Closed-loop identification expansion: the main difference between open and closed loop identification is that the data used in identification process is collected under open-loop or closed-loop condition. Accordingly, if this kind of expansion is adopted, users can easily change the model input from the fixed constant or bolus input to the automatic input (i.e. the controller's output). It is more important that the model identification method should be also changed to meet closed-loop identification need.

2.4 Control operation division

2.4.1 Control division introduction

This simulation platform provides four control modes: manual, automatic, manual + automatic (switching from manual mode to automatic mode), and automatic + manual (switching from automatic mode to manual mode). Each of the four modes has its own simulation significance and usages, such as control performance test and comparison, fault creation and detection, and even simulation training for novice anesthesia residents, etc. Although there are only four types of control modes given in this platform as sampling programs, the abundant connectors allow users to expand the existing control modes to the extent they need, thereby improving the flexibility of the simulation platform.

The four modes could also be condensed into two kinds of operations—manual and automatic operation. For manual operation, users will need to set the infusion mode (constant, bolus or both), the infusion rate or amount and the drug delivery time point in advance. For automatic operation, users will need to employ the separated control algorithm program to determine the drug infusion strategy automatically. As templates and contrasts, two kinds of control algorithms, which are widely used in anesthesia field, were provided in this platform. One is the internal model control based PID method [43] and the other is model predictive control method [44]. Finally, this platform automatically integrates the selected control algorithm with the controlled patient and prints out the diagrams of control effect. In addition, certain faults such as actuator and sensor faults can be incorporated in this division, and some kinds of technologies such as an extended state observer [45] could be developed to help detect and deal with the sensor artifact.

Apart from the above, an alternative scenario loading mode is provided in this platform. In this mode, users can load the scenario files within this platform to have a test run, and they can also compile scenario files themselves to describe specific scenes usually used in future studies. It is worth noting that the scenario loading part and the aforementioned manual/automatic control part are parallel and cannot be used simultaneously.

2.4.2 Control division development

This section is relatively important for the general closed-loop anesthesia researchers because the novelty developed control algorithms should be realized in this division. This control operation division packaged as an m-file called "control_run.m" is essentially a data collection and processing program, and it is also realized based on the virtual

patient division. For the realization of manual operation, the virtual patient division (i.e. "VIRTUAL_SUBJECT.m") is called after the settling of drug infusion strategy, which is simple to process. While for the realization of automatic operation, other separated functions should be programmed to act as closed-loop control algorithms, such as the m-files "controlimc.m" and "controlmpc.m" incorporated in this platform. These closed-loop control programs can be treated as packages that collect and conduct the previous data needed in the algorithms and generate the drug infusion amount in real time. Moreover, the combination of the manual and automatic control algorithms should be based on a switching time provided by the users.

In conclusion, the developing flow of this control operation division can be summarized as following. First, the selected control mode, the selected virtual patient, the running and switching time, and the relevant parameters needed in the control algorithms should be settled in advance. Then the virtual patient division would be called iteratively to simulate the patient in anesthesia process and the chosen drug infusion strategy would be invoked to regulate the controlled patient. Finally, the program would keep the useful process data in mind automatically and plot the corresponding control effect figures.

2.4.3 *Control division expansion*

This division also provides certain expandable functions for users. As alternative options, there are some extension methods shown in the following content.

1. Novel control algorithm expansion: once researchers develop a new control algorithm and want to have a test, the developed control algorithm should be programmed and embedded into this platform. In this platform, as closed-loop control algorithms such as internal model control based PID and model predictive control are separated from the main program, the programming process of the added algorithm seems relatively easy to handle. Users could extract the data necessary to the control algorithm from the virtual patient division via the function ports by imitating the existing sample programs, and then program to deal with the collected data and give out the drug infusion strategy.
2. Control mode expansion: Although there are only four kinds of control modes provided in this platform, users could expand the existing control modes according to their needs. For example, the expansion mode "manual + automatic + manual" could be realized by inserting another switching time point into the main program.

This division is relatively principal and flexible, so the available expansion methods are not merely limited to the above two types. In fact, the core of the model identification and the control operation division deals with the virtual patient with various methods. Therefore, all the other reasonable divisions could also be compatibly incorporated into this platform.

2.5 Platform construction

In the above sections, the functions, usages, developments and expansions of the three primary components in this platform have been detailed separately. In summary, the cores of the three components could be condensed as follows: The virtual patient division is essentially a black box model simulating the virtual patient under anesthesia, aiming to provide certain process data in order to test some control and identification algorithms, etc. The model identification division is actually a data collecting and processing program segment aiming at testing several model identification algorithms, providing identified models for some model-based control algorithms or fault detection methods. And the control operation division is relatively flexible and mainly developed for the researchers to develop and compare several novel control algorithms. The interactions of the three components are shown in Fig. 2.

From Fig. 2, one will see that the virtual patient division could be treated as the foundation of this platform, whereas the other two divisions, which could run separately, are developed to operate on the virtual patients. Such construction, by minimizing the correlations of various components, makes it convenient for users to change, compose, expand and transplant the programs in a flexible platform.

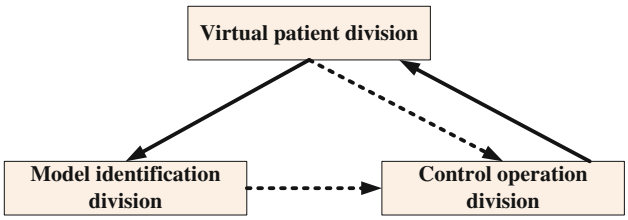

Fig. 2 The interactions of the three primary components in the platform at the view of program development. The dashed lines represent that the corresponding interactions would occur only under certain conditions. The virtual patient division provides simulated data to the model identification division. The control operation division provides drug infusion strategy to the virtual patient division, and the virtual patient division would act on the control operation division in return under closed-loop control condition. When the model-based control algorithm is adopted and the patient's model is not obtained ahead of time, the interaction between model identification division and control operation division would exist. Otherwise, the model identification division and the control operation division would run without interfering with each other

For users, there are several potential but unexplored functions of this platform, and the functions will be explained in the following section.

2.6 Platform potential functions

Apart from the functions existing in this platform, several potential functions could also be achieved by changing or expanding the available programs in this platform. These potential functions are listed as follows.

1. The establishment of synergy model. The available models in the model library are all single input single output models, so the addition of the synergy models could expand the virtual patients from a kind of univariate system to multivariate system.
2. Observer addition and performance evaluation. This platform has already incorporated a kind of extended state observer. Take it as a sample program and other kinds of observers could also be installed into this platform to be used and the observation performances could be compared.
3. Fault creation and detection. Some faults such as artifacts could be simulated and several methods raised to detect and isolate the faults could be realized and compared.
4. Operation stimulus simulation. The stimulus could be treated as a form of disturbance occurring during closed-loop anesthesia that can be realized on the virtual patients.
5. Creation of tutorial software for guiding new anesthesia residents. For this usage, the model library should be further completed.

3 Platform operation example

In Sect. 2, various functions of this simulator have been exhibited and explained. However, for the closed-loop anesthesia researchers, the question of how to develop a novel control algorithm is the most significant. Thus, a brief demonstration will be given in this section about the development and test of a simple control algorithm—PID method. To facilitate the narrative, the following situation will be taken as an example: using BIS as the feedback variable to regulate propofol infusion via manual and PID method.

3.1 PID algorithm development

Throughout the whole control theory, PID control method can be treated as a fundamental, traditional and widely used algorithm. The thought of PID could be concluded as adjusting the controller's output with the deviation of the given set point and the actual system output, and it can be easily formulized as the following equation.

$$u(t) = K_p e(t) + K_i \int e(t)dt + K_d \frac{de(t)}{dt} \tag{11}$$

where K_p, K_i and K_d are the three parameters of the PID controller, and e (t) denotes the derivation of set point and system output.

After discretization, Eq. (11) can be rewritten in an incremental form as Eq. (12).

$$\Delta u(k) = K_p(e(k) - e(k-1)) + K_i e(k) T_S + K_d \frac{e(k) - 2e(k-1) + e(k-2)}{T_s} \tag{12}$$

where T_s is the sampling time, and the meanings of K_p, K_i, K_d and e are the same as those in Eq. (11).

Obviously, the construction of the PID controller is based on the collecting and processing of the deviation data. So the virtual controller program should incorporate the previous input data, output data and set point value as the function input variables, and the controller's output as the function output variable. After that construction, the PID controller program should be embedded into this platform parallel to the other two controllers, and the symbol convenient for choice such as "pid" should also be added to denote this algorithm. Finally, the PID control algorithm option should be added into the user interface in order to active this algorithm.

3.2 PID algorithm test process

The overall structure of this anesthesia simulator has been shown in Fig. 1, and its corresponding user interface which reflects the platform structure intuitively could be found in Fig. 3. As can be seen from Fig. 3, this platform has four parts: (1) "simulation background options" division; (2) "patient model identification" division; (3) "control parameters setting" division, and (4) "virtual patient options and platform launch" division. However, the test of PID algorithm performance only requires three of the aforementioned four divisions, as the PID control method is a model-free algorithm and no need of model identification. Based on the user interface, the following test procedures are given to illustrate the usage of PID virtual controller.

Step 1: Determine the simulation background. In this step, users should set the "Control mode" option as "manual + automatic", set the "Anesthesia indices" option as "hypnosis" and set the "Drugs" option as "propofol".

Step 2: Select the controlled virtual subjects. As an example, two virtual patients, F_adult#003 and

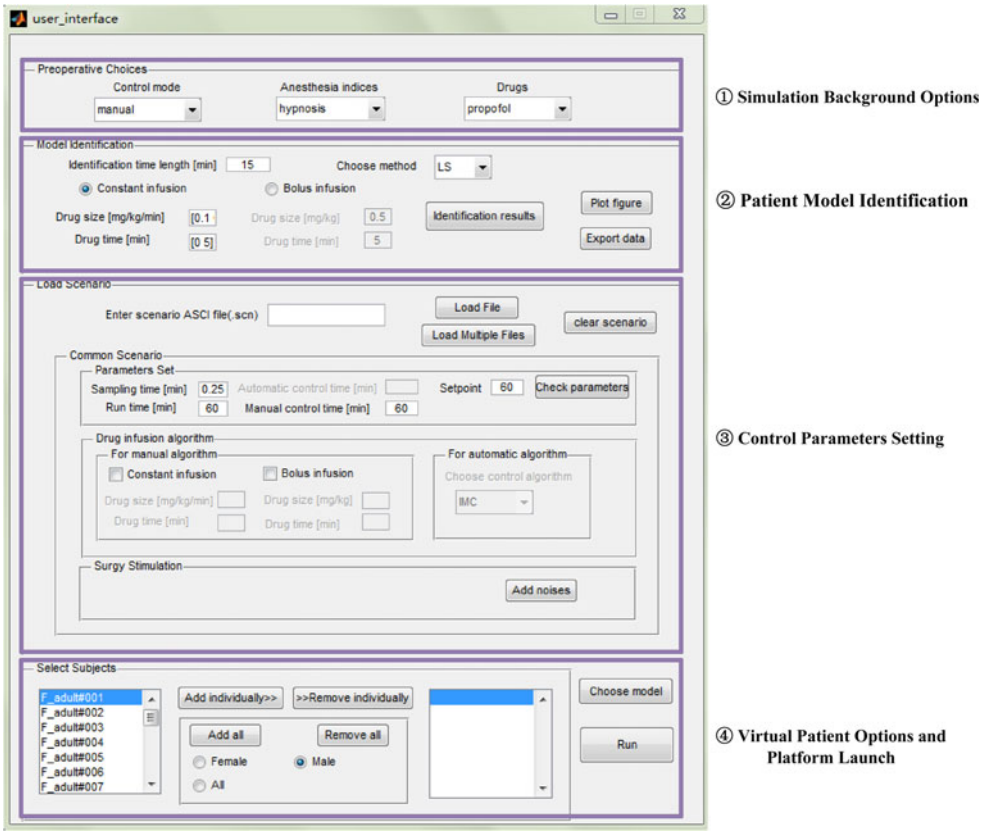

Fig. 3 The user interface of the anesthesia simulator

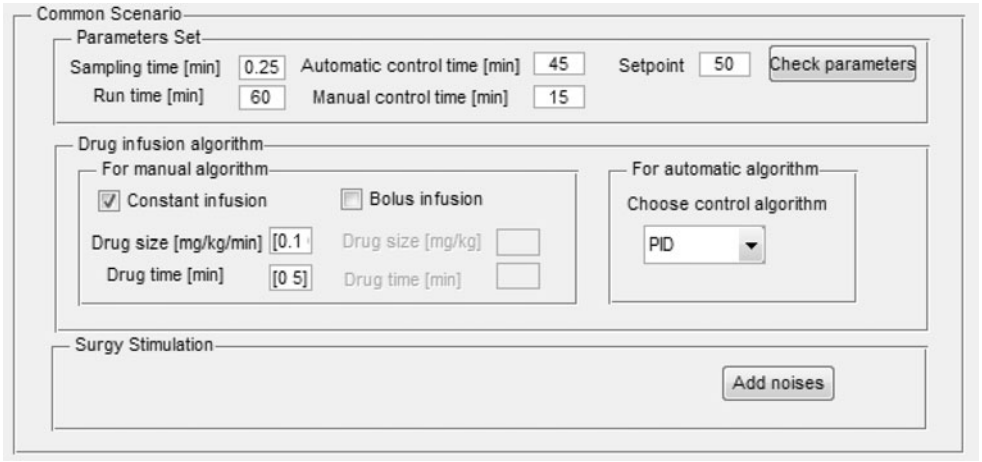

Fig. 4 Control parameters setting configuration

M_adult#014, were chosen. The selected drug model is the three-compartmental PK-PD model for propofol proposed by Schnider et al. [10, 11].

Step 3: Configure the control parameters setting division. In this step, "setting the parameters manually" was used as an example instead of loading the existing scenario files. First, some simulation information, such as sampling time length, run time length, set point value, and automatic and manual control time lengths, should be set. Second, the check boxes of manual drug infusion algorithm should be selected according to actual requirement. Here, the constant infusion control algorithm was selected. For this strategy, the numerical value of drug size was set as 0.1 at the beginning and was changed to 0.25 from the 5th min. Next, PID algorithm was selected, and the corresponding parameters were set as $K_p = -5.3$, $K_i = -3$, $K_d = -0.006$. After these procedures, the control configuration has been completed (See Fig. 4).

Step 4: Launch the platform by pressing the "Run" button. This is the last step of normal operation and the final control results can be found in Fig. 5. The

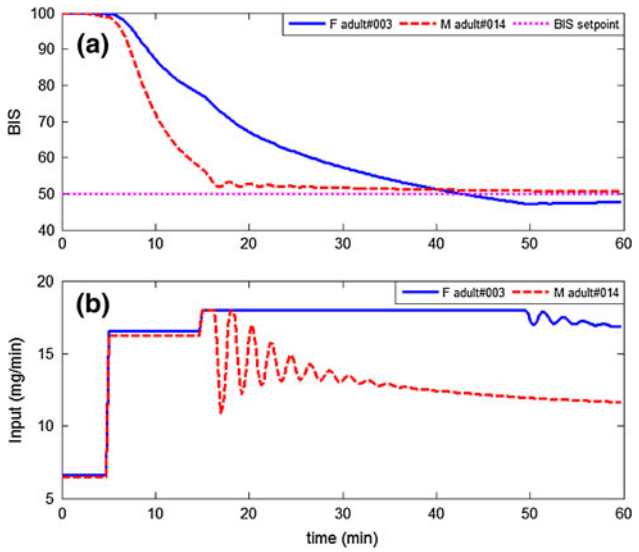

Fig. 5 The control results of two patients (F adult#003 and M adult#014) under PID control. **a** Demonstrates the BIS indices of the two patients; **b** demonstrates the propofol's infusion rates

simulation data can be treated as real data in practical operation and users could obtain the measurement data by pressing the "Add noises" button and completing the configuration according to the actual situation.

4 Conclusions

In this paper, we describe a new enriched anesthesia simulator which we have constructed and introduced. It combines four kinds of widely used anesthesia models into a model library and provides some other additional functions such as model identification, manual/automatic control algorithm trial, noise simulation, etc. This anesthesia simulation platform can save time and simplify development projects for researchers who devote themselves to investigating novel closed-loop anesthesia control algorithms and it can also provide reference value to a certain degree as a small model library. It also shows promise as an educational tool for anesthesia residents by simulating clinical conditions apt to be encountered in the operating room when administering anesthetic drugs.

However, there are some limitations of this platform that are listed as follows.

1. Due to the incorporated models in this platform, the simulator only supports control algorithm developments of univariate systems at present.
2. Under current conditions, this simulator does not include the modeling of relevant stimuli during operation.
3. This simulator is merely a benchmark tool for testing certain control algorithms in vitro before actual clinical experiments, and the practical performances of the controllers still need to be verified via clinical experiments.

In the future, further studies should be done on the basis of this existing platform. First, the model library can be enriched with the development of anesthesia models. Second, to describe practical clinical scenarios more distinctly, a surgery stimulation scenario should be added to this simulation platform. In addition, some other evaluation tools and indices might be included in this simulation platform. Finally, this platform should be refined to reflect actual real-world clinical situations more accurately. These issues will be considered in future studies.

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Conflict of interests The authors declare that they have no conflict of interest.

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