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A Subspace-based Wiener System Identification Method for the Individualized Anesthesia Care ⋆

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Abstract: This study focuses on the individual sedation model identification problem, and proposes a subspace-based Wiener system identification method. The traditional compartmental pharmacokinetics-pharmacodynamics hypnosis model is considered as a specific Wiener system with the Hill equation nonlinear term. To deal with the Hill nonlinear term, the proposed method employs a set of specific bases to turn the Wiener system into a linear one, and then the subspace orthogonal projection identification method has been implemented to identify the transformed linear model. Compared with the traditional anesthesia model identification methods, the proposed method can effectively overcome the shortage of measurement data, get rid of the estimation of the effect compartment concentration which is impossible to be measured, and improve the individualization performance of the identified model. A simulation study on 24 various virtual patients from the Wang's Simulator has been conducted and validates the efficiency and robustness of the proposed method, and a drug infusion instruction has been provided in order to get relatively accurate identification performance.

1. INTRODUCTION

During the clinical surgery operation, an appropriate anesthetic infusion strategy is indispensable to ensure the patients in a narcosis and safety situation. In recent years, the automatic control technique is being applied in the anesthesia field, and appears more and more progressive and prosperous. For the individualized controller designation, the patient information is required as much as possible, and the development of a relatively accurate anesthesia patient model becomes reasonable and imperative. Among the extant various anesthesia pharmacokinetics-pharmacodynamics (PK-PD) modeling methods, compartmental modeling method has been widely applied due to its simplicity, accuracy, and effectiveness. For hypnosis, there are numbers of compartmental PK-PD models (Schnider et al. [1998], Schnider et al. [1999], Schüttler and Ihmsen [2000], and Yasuda et al. [1991]) corresponding to different hypnotics. After considering the mainstream trend and the efficiency used in the target-controlled infusion (TCI) systems (Masui et al. [2010]), the three compartmental PK-PD propofol model proposed by Schnider et al. (Schnider et al. [1998], and Schnider et al. [1999]) was eventually adopted to do the exemplary identification research. From the perspective of system identification, the selected model can be treated as a Wiener system model, which is composed of a third-order linear term and a static nonlinear term–Hill equation, and the studied problem is actually a specific Wiener system identification problem.

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Considering the increasingly prosperous model-based anesthesia control, various compartmental PK-PD models have been used to describe the patients' characteristics. However, in the practical research, there are still some difficulties and unresolved problems about the compartmental PK-PD model identification. In (Sawaguchi et al. [2003]), the compartmental model was separated into PK and PD parts, and the effect compartment concentration was evaluated with the use of TCI equipment in order to facilitate the PD parameter identification. In (Ionescu et al. [2008]) and (Niño et al. [2009]), the empirical nominal patient model was applied to compensate the nonlinearity and predict the future output. Therefore, the existence of the nonlinear term tends to increase the complexity of the individualized model identification, and the partial experience based model could also decrease the individual level and identification accuracy. In addition, because of the limited induction time, the lack of identification data is still an existing notable problem. To alleviate these aforementioned problems, some measures have been taken, such as the novel simplified propofol PK-PD model which is convenient for identification (Hahn et al. [2012]), the extended Kalman filter technique applied to the neuromuscular blockade compartmental model (da Silva et al. [2012]), etc. However, the accuracy and simplicity of the identification method can hardly be satisfied simultaneously. In this situation, a subspace-based identification method has been first employed to solve the extant identification problems in anesthesia field.

The subspace identification technique (Huang et al. [2005], Overschee and De Moor [1995], and Wang and Qin [2002]) is based on the linear time-invariant (LTI) state-space model structure, and the corresponding input-output mea-

surements can be arranged by iteration to deduce the system matrices by different algorithms. Furthermore, several subspace-based Wiener system identification methods (Gómez and Baeyens [2005], and Lovera et al. [2000]) have been proposed. In this work, considering the specific anesthesia Wiener system, a set of selected nonlinear primary functions is employed to turn the Wiener system into a single-input multi-output linear one. After that, the ordinary subspace identification can be used to deal with the general linear identification problem.

From the anesthesia model identification perspective, the proposed method can deal with some existing identification challenges and have the following advantages. First, all the model parameters are identified with the patient's individual measurements, and independent of any empirical model information, so the individual model characteristics would be intensified effectively. Furthermore, the identification results can be derived directly by calculation of the input and output measurements. As a result, the identification efficiency could be improved, and by avoidance of the effect compartment concentration estimation, certain identification inaccuracy would be excluded. Besides, this method provides an alternative to deal with the Hill nonlinearity, and the introduction of series primary functions can moderately contribute to the data addition. Finally, there are also two potential benefits that this method lays the foundation of online identification implementation, and offers a paradigm to some similar identification problems, such as analgesia and neuromuscular blockade.

The rest part of this paper is organized as follows. As the preliminary knowledge, the adopted three compartmental propofol PK-PD model is briefly introduced in Section 2. In Section 3, the proposed subspace-based Wiener system identification algorithm is presented in detail. As the algorithm validation and demonstration, the identification simulation results are illustrated in Section 4. Finally, the conclusion is concluded in Section 5.

2. PRELIMINARY KNOWLEDGE

In this study, the propofol PK-PD compartmental model developed by Schnider et al. (Schnider et al. [1998], and Schnider et al. [1999]) was employed to do the identification research as an archetype. The proposed model illustrated in Fig. 1 has a serial structure of two separated parts–the PK and PD parts. Based on the mass balance theory, the PK part can be modeled by third-order linear differential equations, and the PD part can be represented as a first-order differential equation plus a static nonlinear Hill equation term. Therefore, the integrated three-compartmental propofol model could be regarded as a Wiener system model.

In detail, the PK part is modeled as the following state-space model.

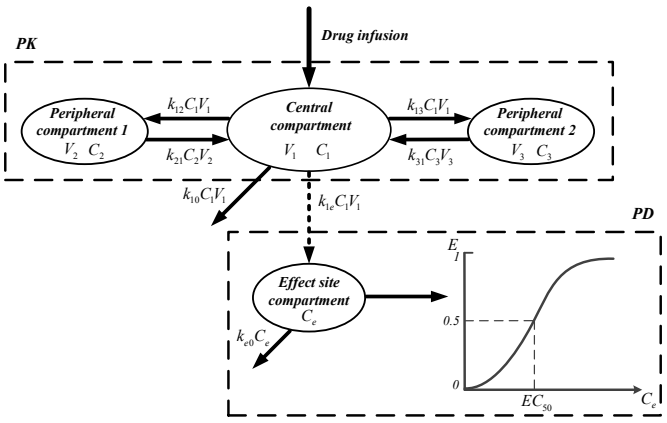

Fig. 1. Schnider propofol three-compartmental PK/PD model structure.

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

where C_1, C_2 and C_3 denote the drug concentration in the central compartment, peripheral compartment one and two, respectively. V_i $(i = 1, 2, 3)$ denote the volume of the ith compartment, the constants k_{ij} $(i, j = 1, 2, 3,\ i \neq j)$ indicate the drug amount transfer rate from the ith compartment to the jth one, the constant k_{10} indicates the drug metabolism rate, and $u(t)$ is the propofol infusion rate. For the Schnider propofol population model, some other personalized parameters in the PK part can be found in (Ionescu et al. [2008]).

The PD part aims to make a combination of the drug concentration and the drug effect. According to the mass balance theory, the effect compartment can be modeled by (2) (Ionescu et al. [2008])

$$\frac{dC_e(t)}{dt} = k_{e0}(C_1(t) - C_e(t)) \tag{2}$$

where the constant k_{e0} reflects the transfer ratio between the central compartment and the effect compartment, and C_e is the drug concentration of the effect compartment.

Concerning the Hill equation, which describes the relationship between C_e and the drug effect–bispectral index (BIS), its mathematical expression is represented in (3)

$$BIS(t) = BIS_0 - BIS_{\max}\frac{C_e^{\gamma}(t)}{C_e^{\gamma}(t) + EC_{50}^{\gamma}} \tag{3}$$

where BIS_0 and $BIS_{\max}$ denote the baseline and maximum effect value of BIS, respectively, which are typically assigned a value of 100. Here, EC_{50} is the drug concentration at half maximal effect, and γ determines the steepness of the Hill equation curve. The patients' PD characteristics are reflected individually by EC_{50} and γ.

As a whole, in the aforementioned continuous-time Wiener model, k_{ij} $(i,j = 1,2,3,\ i \neq j)$, k_{10}, k_{e0}, V_i $(i = 1,2,3)$, EC_{50}, and γ are the unknown individualized parameters. For the convenience of subspace identification and control conduction, the continuous-time model should be transformed into the corresponding discrete model. In this case, the forward difference method was employed to deal with the differential terms and obtain the following discrete Wiener model.

$$\begin{aligned} x(k+1) &= Ax(k) + Bu(k) \\ y(k) &= Cx(k) \\ BIS(k) &= BIS_0 - BIS_{\max}\frac{y(k)^\gamma}{y(k)^\gamma + EC_{50}^\gamma} \end{aligned} \tag{4}$$

where $x(k) = (\ C_1(k)\ C_2(k)\ C_3(k)\ C_e(k)\ )^T$ is the system state vector, $y(k)$ denotes $C_e(k)$, and k represents the k^{th} sample point. Considering the transformed discrete model, the system matrices A, B, C, variables EC_{50} and γ are the unknown individualized parameters.

3. SUBSPACE-BASED ANESTHESIA WIENER SYSTEM IDENTIFICATION

3.1 Subspace identification method

To make this paper self-contained, a brief introduction about the subspace orthogonal projection identification method (Huang et al. [2005]) will be given in the subsection. First, consider the following discrete state-space model in the innovation form

$$\begin{aligned} x(k+1) &= Ax(k) + Bu(k) + Ke(k) \\ y(k) &= Cx(k) + Du(k) + e(k) \end{aligned} \tag{5}$$

where $x(k) \in R^n$, $u(k) \in R^m$, and $y(k) \in R^q$ represent the plant states, inputs and outputs, respectively; $e(k) \in R^q$ is the white noise innovation sequence with covariance Σ_e ; the matrices A, B, C, D are the system matrices; K is the disturbance parameter.

Via the iterative substitution procedures of (5), the following compact subspace matrix equations can be derived.

$$\begin{aligned} Y_f &= \Gamma_i X_f + H_i^d U_f + H_i^s E_f \\ Y_p &= \Gamma_i X_p + H_i^d U_p + H_i^s E_p \end{aligned} \tag{6}$$

where the subscripts p and f represent "past" and "future", severally. The past and future input block-Hankel matrices U_p and U_f in (6) are defined as follows.

$$U_p = \begin{pmatrix} u(0) & u(1) & ... & u(j-1) \\ u(1) & u(2) & ... & u(j) \\ ... & ... & ... & ... \\ u(i-1) & u(i) & ... & u(i+j-2) \end{pmatrix} \tag{7}$$

$$U_f = \begin{pmatrix} u(i) & u(i+1) & ... & u(i+j-1) \\ u(i+1) & u(i+2) & ... & u(i+j) \\ ... & ... & ... & ... \\ u(2i-1) & u(2i) & ... & u(2i+j-2) \end{pmatrix} \tag{8}$$

where $U_p,\ U_f \in R^{mi\times j}$, and i, j are the user-defined dimensions. Note: The row dimension of matrix U_f is not required to be the same as that of U_p. Similarly, the past and future output and innovation block-Hankel matrices Y_p, Y_f, E_p, and E_f are defined conformably with U_p and U_f. The state sequences X_p and X_f are defined as follows.

$$X_p = (\ x(0)\ x(1)\ ...\ x(j-1)\ ) \tag{9}$$

$$X_f = (\ x(i)\ x(i+1)\ ...\ x(i+j-1)\ ) \tag{10}$$

where $X_p,\ X_f \in R^{n\times j}$.

In (6), the extended observability matrix Γ_i , the lower triangular block-Toeplitz matrices H_i^d and H_i^s , are given as follows.

$$\Gamma_i = \begin{pmatrix} C^T & (CA)^T & ... & (CA^{i-1})^T \end{pmatrix}^T \tag{11}$$

$$H_i^d = \begin{pmatrix} D & 0 & 0 & ... & 0 \\ CB & D & 0 & ... & 0 \\ CAB & CB & D & ... & 0 \\ ... & ... & ... & ... & ... \\ CA^{i-2}B & CA^{i-3}B & CA^{i-4}B & ... & D \end{pmatrix} \tag{12}$$

$$H_i^s = \begin{pmatrix} I & 0 & 0 & ... & 0 \\ CK & I & 0 & ... & 0 \\ CAK & CK & I & ... & 0 \\ ... & ... & ... & ... & ... \\ CA^{i-2}K & CA^{i-3}K & CA^{i-4}K & ... & I \end{pmatrix} \tag{13}$$

where $\Gamma_i \in R^{qi\times n}$, $H_i^d \in R^{qi\times mi}$, and $H_i^s \in R^{qi\times qi}$.

The major aim of the proposed method is to eliminate the unknown terms E_f (or E_p) and X_f (or X_p) in (6). Obviously, the future noise matrix E_f is independent of the past input and output data, so the past data combination $W_p = (Y_p^T\ U_p^T)^T$ is selected as the projection instrumental variable. As a result, the orthogonal projection of E_f onto W_p is zero. After that, for the first equation in (6), the term $H_i^d U_f$ is moved to the left-hand side as below.

$$\begin{bmatrix} I & -H_i^d \end{bmatrix} W_f/W_p = \Gamma_i X_f/W_p \tag{14}$$

where $W_f = \begin{pmatrix} Y_f^T & U_f^T \end{pmatrix}^T$. On the basis of (14), by pre-multiplying both sides with $(\Gamma_i^\perp)^T$, the orthogonal column space complement of Γ_i, the final result is

$$(\Gamma_i^\perp)^T \begin{bmatrix} I & -H_i^d \end{bmatrix} W_f/W_p = 0 \tag{15}$$

The left null space of the matrix $L = W_f/W_p$ is composed of the system matrices A, B, C, D. To derive the system information, the singular value decomposition (SVD) technique is applied onto L as

$$L = (\ U_1\ U_2\ ) \begin{pmatrix} \Sigma_1 & \\ & 0 \end{pmatrix} \begin{pmatrix} V_1^T \\ V_2^T \end{pmatrix} \tag{16}$$

The left null space of L can be derived as

$$\left((\Gamma_i^\perp)^T \begin{bmatrix} I & -H_i^d \end{bmatrix}\right)^T = U_2 \tag{17}$$

Then divide U_2 into $\begin{pmatrix} P_1^T & P_2^T \end{pmatrix}^T$, and (17) can be rewritten as

$$\begin{pmatrix} \Gamma_i^\perp \\ -(H_i^d)^T\Gamma_i^\perp \end{pmatrix} = \begin{pmatrix} P_1 \\ P_2 \end{pmatrix} \tag{18}$$

According to (18), the matrices Γ_i and H_i^d could be derived as

$$\begin{aligned} \Gamma_i &= P_1^\perp \\ -(P_1)^T H_i^d &= P_2^T \end{aligned} \tag{19}$$

Then the system matrices A, B, C, D can be extracted from Γ_i and H_i^d (Wang and Qin [2002]).

3.2 Anesthesia Wiener system identification

Based on the preparation knowledge in the preceding sections, the subspace-based identification method of the Schnider propofol Wiener model will be described as below. First, consider the discrete Wiener model in (4). With prior knowledge, the system matrix D is set as zero ahead of time. Comparing the linear part of (4) with the normal state-space model in (5), there is no noise term

$e(k)$. Because in the anesthesia process, the measurement noise ususlly appears on the measured BIS value, several filter techniques can be employed to eliminate it. However, in this paper, the specific filter technique was not taken into consideration, and will be discussed in the future work. Therefore, the disturbance parameter K is equal to zero.

The difficulty of identification is how to deal with the static nonlinear term of the Wiener system. From experience, the parameters BIS_0 and $BIS_{\max}$ are usually set as 100, so the Hill equation in (4) will be transformed as

$$BIS(k) = 100 \times \frac{EC_{50}^{\gamma}}{(y(k))^{\gamma} + EC_{50}^{\gamma}} \tag{20}$$

According to (20), the intermediate variable $y(k)$ can be solved as

$$y(k) = EC_{50} \cdot \left(\frac{100}{BIS(k)} - 1 \right)^{\frac{1}{\gamma}} = EC_{50} \cdot BIS_{cal}(k)^{\frac{1}{\gamma}} \tag{21}$$

Substitute it into the linear part of (4), the following compact nonlinear state-space form can be derived.

$$\begin{aligned} x(k+1) &= Ax(k) + Bu(k) \\ EC_{50} \cdot BIS_{cal}(k)^{\frac{1}{\gamma}} &= Cx(k) \end{aligned} \tag{22}$$

Because the aforementioned subspace identification method can be merely used in the linear system, the linearization procedure should be taken to deal with the crucial nonlinear term $EC_{50} \cdot BIS_{cal}^{\frac{1}{\gamma}}$. To do the linearization, a set of basis functions with known powers has been selected, and its linear combination has been conducted to approximate the nonlinear term as

$$\begin{aligned} EC_{50} \cdot BIS_{cal}^{\frac{1}{\gamma}} = EC_{50} \cdot (a_0 BIS_{cal}^{\frac{1}{\gamma_0}} + a_1 BIS_{cal}^{\frac{1}{\gamma_0}+\Delta} + \dots \\ + a_N BIS_{cal}^{\frac{1}{\gamma_0}+\Delta \cdot N}) = \sum_{i=0}^{N} \alpha_i BIS_{cal}^{\frac{1}{\gamma_0}+\Delta \cdot i} \end{aligned} \tag{23}$$

where Δ is the searching step size; $\left[\frac{1}{\gamma_0}, \ \frac{1}{\gamma_0} + \Delta \cdot N \right]$ is the estimated range of the parameter $\frac{1}{\gamma}$ set by experience; the parameter vector $\alpha = (\ \alpha_0 \ \dots \ \alpha_N\ )$ includes the weight factors of the corresponding basis functions.

After the transformation, substitute (23) into (22), the original Wiener model is changed as

$$\begin{aligned} x(k+1) &= Ax(k) + Bu(k) \\ (\ \alpha_0 \ \dots \ \alpha_N\ ) \begin{pmatrix} (BIS_{cal}(k))^{\frac{1}{\gamma_0}} \\ \dots \\ (BIS_{cal}(k))^{\frac{1}{\gamma_0}+\Delta \cdot N} \end{pmatrix} &= Cx(k) \end{aligned} \tag{24}$$

Compare (24) with (22), the crucial change is that the unknown power term $\frac{1}{\gamma}$ is replaced by a series of known power terms. To keep constant with the normal state space form in (5), the new system can be further converted into

$$\begin{aligned} x(k+1) &= Ax(k) + Bu(k) \\ \left((BIS_{cal}(k))^{\frac{1}{\gamma_0}} \ \dots \ (BIS_{cal}(k))^{\frac{1}{\gamma_0}+\Delta \cdot N} \right)^T &= \tilde{C}x(k) \end{aligned} \tag{25}$$

where the matrix $\tilde{C}$ comprehends the inverse of the vector α. In this form, the primary single-input single-output (SISO) Wiener system has been changed into a single-input multiple-output (SIMO) LTI system. Hence, the above converted LTI state-space system can be properly identified using the subspace orthogonal projection identification method.

After the subspace identification procedures, the system matrices A, B, and $\tilde{C}$ can be calculated. Then, the next problem is how to extract the estimations of the matrices C and α from $\tilde{C}$. As a matter of fact, the best estimations (in the mean squares sense) of C and α satisfy the following minimization problem as

$$\left(\hat{C}, \ \hat{\alpha}^{\dagger} \right) = \arg \min_{C, \ \alpha^{\dagger}} \left\{ \left\| \hat{\tilde{C}} - \alpha^{\dagger} C \right\|_2^2 \right\} \tag{26}$$

where the symbol $\alpha^{\dagger}$ represents the left pseudoinverse of α. The solution to the minimization problem in (26) is provided by the SVD of the matrix $\hat{\tilde{C}}$ (Gómez and Baeyens [2005]). Eventually, the unknown system matrices A, B, C, and α in (24) can be worked out. Because the identified SIMO system ought to be converted back to the primary SISO system, a nonlinear curve reflecting the relationship between y and BIS was portrayed with the information of $\hat{\alpha}$. When there is one value of y, the corresponding BIS value can be looked up according to the curve. In summary, the integral subspace-based Wiener system identification method will be summarized as follows.

Step 1: Process the Hill equation as in (23), and construct the SIMO LTI system in (25).

Step 2: Collect the input and output measurement data, and stack the data into the block-Hankel matrix as the matrix L introduced in subsection 3.1.

Step 3: Do SVD on L as (16), calculate the matrices Γ_i, H_i^d as (17)-(19), and extract the estimations of the system matrices A, B, and $\tilde{C}$.

Step 4: Compute the economy-size SVD as $\hat{\tilde{C}} = U_s \Sigma_s V_s^T$, and make a partition of the decomposition as

$$\hat{\tilde{C}} = (\ U_a \ U_b\ ) \begin{pmatrix} \Sigma_a & 0 \\ 0 & \Sigma_b \end{pmatrix} \begin{pmatrix} V_a^T \\ V_b^T \end{pmatrix} \tag{27}$$

where $\Sigma_a = \sigma_1$, $U_a \in R^{(N+1)\times 1}$, $V_a \in R^{n \times 1}$.

Step 5: Calculate the estimations of the system matrices C and α as $\hat{C} = \Sigma_a V_a^T$, $\hat{\alpha} = U_a^{\dagger}$, which is a unitary vector. Because of the unitary characteristic, the output of the identified linear model in (24) is proportional to the effect compartmental concentration C_e.

Step 6: Portray the look-up nonlinear curve according to the identified parameter $\hat{\alpha}$, and find out the corresponding BIS value via the model output in (24).

For the proposed subspace-based identification method in this paper, there are several practical significances, such as prediction, model-based control conduction, etc. Besides, there are some advantages over certain extant anesthesia model identification methods as well. For instance, this method needs no priori knowledge of the patients and model, no rigorous requirment of data amount, and also has the potential to process the closed-loop identification and on-line control problems, which can direct the drug infusion rate. Finally, the identification result, in a state-space model form, is advantageous to developing the model-based control algorithm.

4. SIMULATION RESULTS AND ANALYSIS

To test the accuracy and robustness of the proposed identification method and ensure the patients' security, a series of simulation experiments have been proformed on the Wang's anesthesia simulator (Fang et al. [2013]) in advance. In this anesthesia simulator, 24 virtual patients with different clinical characteristics are available. First, the proposed method was conducted, tested and analysed on the virtual patient "F_adult#001" in the experimental scenarios without and with measurement noise. According to the identification performances, a proper propofol infusion instruction has been given out. Finally, as an extension, that instruction was practiced on the rest 23 virtual patients, and the corresponding results have been also represented.

During the whole simulation experiment, the identification duration and sampling period were set as 10 minutes and 15 seconds, respectively. Here, the system parameters γ_0, Δ, and N were fixed as 6, 0.1 and 5, severally. First, considering the virtual patient F_adult#001, a 2mg/kg bolus of propofol was infused at the 3^{rd} minute. After identification, the parameter α could be seized, and the nonlinear output BIS were therewith recovered according to the unique personalized nonlinear curve (shown in Fig. 2) and the identified LTI system.

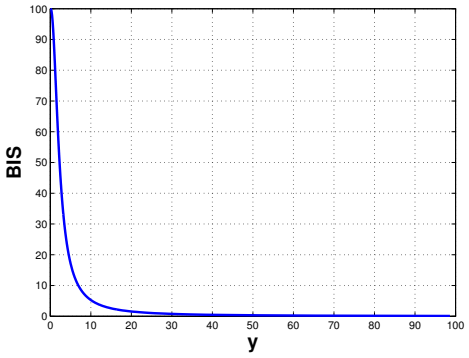

Fig. 2. The nonlinear relationship between y and BIS

After the bolus infusion identification, a constant infusion step signal, with 0.1mg/kg/min at the beginning and changed to 0.3mg/kg/min from the 5^{th} minute, was applied to investigate the extrapolation behaviour of the identified model. Furthermore, to confirm the robustness of the proposed identification method, a random Gaussian white noise with one standard deviation was added onto BIS as measurement noise. In Fig. 3, both of the identification and extrapolation test performances with and without measurement noise have been described.

In the ideal case, the identification performance is well and stable. But during actual clinical operation, the measurement noise is a troublesome but critical term. To ensure the identification accuracy, an optimal drug infusion instruction should be concluded after comprehensively investigating the relationship between the bolus infusion and identification performance with different measurement noise. With regard to the simulation, three kinds of Gaussian white noise were selected to simulate the measurement noise. Because of the randomness, for each situation, 100

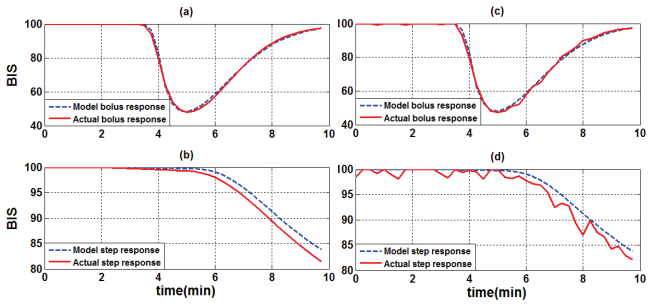

Fig. 3. The identification and extrapolation test performances of F_adult#001. The subfigures (a) and (c) are the identification bolus response fitting curves under the ideal and noise circumstance, respectively. And the subfigures (b) and (d) reflect the corresponding step extrapolation test performances with and without measurement noise, severally.

Monte Carlo experiments were conducted on F_adult#001, and the mean relative error (MRE) index was applied to evaluate the identification accuracy. The final result has been concluded in Table 1.

From the test results established in Table 1, one can see deeper anesthesia contributes to more accurate identification. But it does not mean only high enough bolus dose could arrive at a precise identification. Because it all depends on the noise amplitude, and the ideal identification can be achieved when the system information is much more prominent than the noise signal. Furthermore, the large measurement noise would be usually preprocessed. Therefore, for bolus infusion, the lowest BIS range [40, 50] would be beneficial to a stable and precise identification, even for the largest measurement noise. Hence, before identification, noise analysis is necessary. If no noise analysis, the "safe range" [40, 50] of the lowest BIS value is suggested for bolus infusion. As a matter of fact, the bolus excitation is not exclusively efficient, and due to the characteristic of the proposed method, more input excitation will lead to better identification effect. According to the aforementioned instruction, the identification performance of the rest 23 virtual patients is summarized in Table 2.

5. CONCLUSIONS

In this paper, a subspace-based Wiener system identification method has been presented and first applied to the patient sedation model identification. With this method, the nonlinearity of the Hill term has been resolved without any empirical knowledge. Moreover, it is also effective to solve the data shortage, increase the calculation efficiency, and prepare for some other potential usages such as closed-loop identification and online model-based control conduction. A relatively precise measurement will conduce to a relatively exact identification, which will result in a better prediction and closed-loop control contribution. By simulation, the efficiency and robustness of the proposed method have been demonstrated, and a drug infusion instruction was investigated and given out. As a summary, the proposed identification method can achieve a relatively satisfactory performance, and act as an enlightening method in the anesthesia research field.

Table 1. The identification performance of F_ adult#001 under different kinds of measurement noise and bolus infusion. MRE denotes the mean relative error

Noise amplitude	[-1.5,+1.5]	[-3,+3]	[-6,+6]	
Bolus infusion	MRE	MRE	MRE	Lowest BIS
1mg/kg	0.0754	0.1138	0.1549	87
1.5mg/kg	0.0564	0.0777	0.1220	66
2mg/kg	0.0524	0.0726	0.1170	48
2.2mg/kg	0.0529	0.0761	0.1094	40

Table 2. The identification performance of the rest 23 virtual patients with [-3, +3] measurement noise

Patient	MRE	Patient	MRE	Patient	MRE	Patient	MRE
2	0.0686	8	0.0851	14	0.0940	20	0.0813
3	0.0747	9	0.0824	15	0.0870	F_ nominal	0.0730
4	0.0610	10	0.0924	16	0.0880	M_ nominal	0.0879
5	0.0896	11	0.0969	17	0.0969	F_ average	0.0707
6	0.0747	12	0.0897	18	0.0778	M_ average	0.0715
7	0.0685	13	0.0808	19	0.0878		

REFERENCES

M.M. da Silva, T. Wigren, and T. Mendonça. Nonlinear identification of a minimal neuromuscular blockade model in anesthesia. *IEEE Transactions on Control Systems Technology*, 20:181-188, 2012.

M. Fang, Y. Tao, and Y. Wang. An enriched simulation environment for evaluation of closed-loop anesthesia. *Journal of Clinical Monitoring and Computing*, 28:13-26, 2014.

J.C. Gómez, and E. Baeyens. Subspace-based identification algorithms for hammerstein and Wiener models. *European Journal of Control*, 11:127-136, 2005.

J.-O. Hahn, G.A. Dumont, and J.M. Ansermino. A direct dynamic dose-response model of propofol for individualized anesthesia care. *IEEE Transactions on Biomedical Engineering*, 59:571-578, 2012.

B. Huang, S.X. Ding, and S.J. Qin. Closed-loop subspace identification: An orthogonal projection approach. *Journal of Process Control*, 15:53-66, 2005.

C.M. Ionescu, R. De Keyser, B.C. Torrico, T. De Smet, M. Struys, and J.E. Normey-Rico. Robust predictive control strategy applied for propofol dosing using BIS as a controlled variable during anesthesia. *IEEE Transactions on Biomedical Engineering*, 55:2161-2170, 2008.

M. Lovera, T. Gustafsson, and M. Verhaegen. Recursive subspace identification of linear and non-linear Wiener state-space models. *Automatica*, 36:1639-1650, 2000.

K. Masui, R.N. Upton, A.G. Doufas, J.F. Coetzee, T. Kazama, E.P. Mortier, and M.M.R.F. Struys. The performance of compartmental and physiologically based recirculatory pharmacokinetic models for propofol: A comparison using bolus, continuous, and target-controlled infusion data. *Anesthesia & Analgesia*, 111:368-379, 2010.

J. Niño, R. De Keyser, S. Syafiie, C. Ionescu, and M. Struys. EPSAC-controlled anesthesia with online gain adaptation. *International Journal of Adaptive Control and Signal Processing*, 23:455-471, 2009.

Y. Sawaguchi, E. Furutani, G. Shirakami, M. Araki, and K. Fukuda. A model predictive sedation control system under total intravenous anesthesia. *Proceedings of the IEEE EMBS Asian-Pacific Conference in Biomedical Engineering*, pages 358-359, 2003.

T.W. Schnider, C.F. Minto, P.L. Gambus, C. Andresen, D.B. Goodale, S.L. Shafer, and E.J. Youngs. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology*, 88:1170-1182, 1998.

T.W. Schnider, C.F. Minto, S.L. Shafer, P.L. Gambus, C. Andresen, D.B. Goodale, and E.J. Youngs. The influence of age on propofol pharmacodynamics. *Anesthesiology*, 90:1502-1516, 1999.

J. Schüttler, and H. Ihmsen. Population pharmacokinetics of propofol: A multicenter study. *Anesthesiology*, 92:727-738, 2000.

P. Van Overschee, and B. De Moor. A unifying theorem for three subspace system identification algorithms. *Automatica*, 31:1853-1864, 1995.

J. Wang, and S.J. Qin. A new subspace identification approach based on principal component analysis. *Journal of Process Control*, 12:841-855, 2002.

N. Yasuda, S.H. Lockhart, E.I. Eger II, R.B. Weiskopf, J. Liu, M. Laster, S. Taheri, and N.A. Peterson. Comparison of kinetics of sevoflurane and isoflurane in humans. *Anesthesia & Analgesia*, 72:316-324, 1991.