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Identification of Wiener Models with Anesthesia Applications[1]

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Abstract Wiener structures are employed for modeling a patient's dynamic response to drug infusion in anesthesia applications. The Wiener model structure is first evaluated for its suitability in this application using clinical data. Appropriate parametrization of Wiener models is investigated in terms of its utility in system identification. Recursive identification of Wiener model parameters with parameter constraints is studied in the presence of random disturbances, model mismatch, and unmodeled dynamics. Convergence, rates of convergence, and error bounds on parameter estimation and output prediction are derived. Simulation and application cases are also presented.

Key Words: Anesthesia, Wiener models, identification, stochastic approximation, constrained algorithms, model mismatch, unmodeled dynamics.

1 Introduction

Real-time anesthesia decisions are exemplified by general anesthesia for attaining an adequate anesthetic depth (consciousness level of a patient), ventilation control, etc. One of the most critical requirements in this decision process is to predict the impact of the inputs (drug infusion rates, fluid flow rates, ventilator mode, etc.) on the outcomes (consciousness levels, blood pressures, heart rates, airway pressures, and oxygen saturation, etc.). This prediction capability can be used for control, display, warning, predictive diagnosis, decision analysis, outcome comparison, etc.

The core function of this prediction capability is embedded in establishing a reliable model that relates the drug or procedure inputs to the outcomes in real-time and in individual patients. The underlying problem is a real-time identification problem. For anesthesia applications, the input signals usually include drug infusion rates from digital programmable infusion pumps. The patient response and

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conditions are measured by the bispectral (BIS) monitor for anesthesia depth, the vital sign monitor (such as electrocardiogram (ECG/EKG), blood pressures, oxygen saturation, etc.). In [21, 22] we have tested the validity of the Wiener structure in representing patient dynamics. This model structure represents a system by a dynamic linear part, followed by a memoryless nonlinear function. In anesthesia applications, the dynamic part captures the transient behavior such as time delay and transient time constant, and the nonlinear part models the steady-state sensitivity of the drug response.

This paper will be focused on real-time identification algorithms for Wiener models and their basic properties such as accuracy, computational efficiency, convergence, and rates of convergence. Mathematically, a Wiener model is given by

$$\begin{cases} y_k = h(x_k) + \overline{w}_k, \\ x_k = \overline{\phi}_k^T \overline{\theta} + \widetilde{\phi}_k^T \theta_u + v_k. \end{cases} \tag{1}$$

where $h(\cdot)$ represents static nonlinearity. The dynamic part is given by the difference equation in a regression form; $\overline{\phi}_k^T = [u_k, u_{k-1}, \ldots, u_{k-n}]$ is the principal regressor, $\overline{\theta}$ is the model parameter vector, and $\widetilde{\phi}_k^T = [u_{k-n-1}, \ldots]$ and θ_u represent unmodeled dynamics satisfying $\|\theta_u\|_1 \leq \varepsilon$ where $\|\cdot\|_1$ being the standard ℓ^1 norm, and $\overline{w}_k$ and v_k are mutually independent and independent and identically distributed (i.i.d.) sequences. Only u and y are measured; x is an intermediate variable that cannot be directly measured. The system is assumed to be BIBO (bounded input bounded output) stable, namely, $\|\overline{\theta}\|_1 + \|\theta_u\|_1 < \infty$.

Generally speaking, identification of this Wiener model is a nonlinear problem that can be computationally quite challenging. One possible approach for reducing complexity is to use a special parametrization to represent the inverse of the nonlinear part so that efficient recursive identification algorithms can be applied. This parameterization introduces several essential theoretical issues: (1) Noise features change drametically; (2) Model mismatch on the nonlinear function and unmodeled dynamics on the dynamic part are inevitable since the model is data driven and information-oriented, rather than derived from detailed underlying physical structures.

Impact of such model uncertainties on parameter estimation and output prediction will be studied in this paper. We will establish convergence, rate of convergence, and error bounds of the estimates under stochastic disturbances, model mismatches, and unmodeled dynamics for Wiener models.

The research effort to develop computer-aided drug infusion systems has been both intensive and extensive since the early 1950s. The reader is referred to [3, 4, 9, 12, 14, 32] for control applications in anesthesia depth. The approach of using

Wiener models to represent patient dynamics in anesthesiology was introduced by this team [21, 22, 23, 24].

System identification and recursive algorithms have been an active research field for several decades [10, 11, 7]. In particular, system identification of nonlinear systems has been studied in many model structures. The reader is referred to [18] for a recent overview and its extensive literature citation. Within nonlinear system identification, Wiener/Hammerstein structures have drawn great attention due to their structure simplicity and connections to linear systems [17, 19]. Several identification algorithms are analyzed in [29] for their convergence and error bounds. Frequency-domain identification methods for Wiener/Hammerstein models were explored in [1, 20]. The theoretical findings of this paper are new results on convergence, convergence rates, and error bounds under joint stochastic disturbances, model mismatch, and unmodeled dynamics. Some of the results are extensions from our early conference papers [21, 23, 24].

The remaining part of this paper is organized as follows. Section 2 assesses the utility of Wiener models in representing patient dynamics in anesthesia applications. Section 3 employs a special parametrization of the system by modeling the inverse nonlinear function (rather than the function itself), and formulates the resulting identification problems. Identification algorithms are presented in Section 4. We start with a parametrization of the inverse nonlinear function as a linear combination of nonlinear base functions. This leads to a joint linear identification problem. The properties of the identification algorithms are analyzed in Section 5. This section is devoted to convergence analysis for the identification algorithms under joint stochastic disturbances, model mismatch, and unmodeled dynamics. Some potential extensions are remarked in Section 6. Section 7 presents a case study of patient model identification in anesthesia applications. A brief summary of the findings of this paper is presented in Section 8.

2 Motivating Applications of Wiener Models in Anethesiology

It is a great challenge to characterize a patient's response to drug infusion mathematically. Due to significant deviations in physical conditions, ages, metabolism, pre-existing medical conditions, and surgical procedures, patient dynamics demonstrate high nonlinearity and large variations in their responses to drug infusion. Physiology-oriented models are usually too complicated to establish individually using limited clinical data from a patient. On the other hand, anesthesiologists have been administering drug infusion successfully with only limited information on patients, such as weights and medical conditions. Control strategies of an experienced anesthesiologist are based intuitively on basic characteristics, such as how sensitive the patient is to a drug infusion.

A basic information-oriented model structure for patient responses to drug infusion was introduced in [21, 23]. Propofol (a common anesthesia drug) titration is administered by an infusion pump. The patient's anesthesia depth is measured by a BIS (Bi-Spectrum) monitor. The monitor provides continuously an index in the range of $[0, 100]$ such that the lower the index value, the deeper the anesthesia state. Hence, an index value 0 will indicate"brain dead" and 100 will be "awake". The dynamics of a patient's BIS response to a drug infusion can be divided into several blocks. The response from the titration command to the drug infusion at the needle point is the infusion pump dynamics and can be represented by a transfer function $G_i(s)$. Similarly, the BIS monitor dynamics can be represented by a transfer function $G_m(s)$. The patient dynamics is a nonlinear system. Although the actual physiological and pathological features of the patient require models of high complexity, for prediction or control purposes it is not only convenient but essential to use simple models as long as they are sufficiently rich to represent the most important properties of the patient response. Understanding the information used by anesthesiologists in infusion control, we characterize the patient response to propofol titration with three basic components: (1) Initial time delay τ_p after drug infusion: During this time interval after a change of the infusion rate, the BIS value does not change due to time required for drugs to reach the target tissues, to complete volume distribution. (2) Dynamic reaction: This reflects how fast the BIS value will change once it starts to respond, and is modeled by a transfer function $G_p(s)$. (3) A nonlinear static function for sensitivity of the patient to a drug dosage at steady state: This is represented by a function or a look-up table f. The meanings of these three components can be explained, in a simplistic manner, by a step response, as depicted in Figure 1.

Consequently, a model structure for titration response is shown in Figure 2, which is called Wiener models in the control community. The model parameters vary dramatically among patients and must be established individually for each patient.

To verify the utility of the Wiener model structure in anesthesiology, clinical data were collected. One of these data sets is used to illustrate the process and results here.

The anesthesia process lasted about 76 minutes, starting from the initial drug administration and continuing until last dose of administration. Propofol was used in both titration and bolus. Fentanal was injected in small bolus amount three

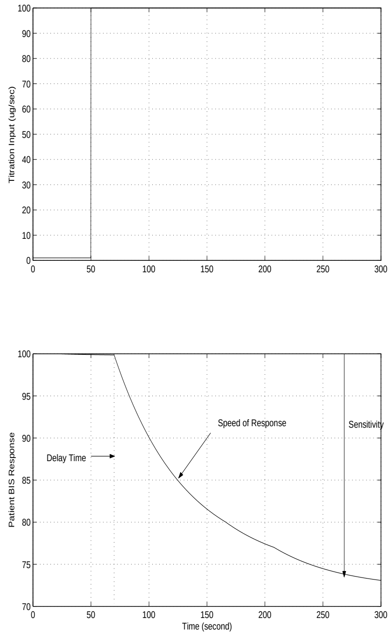

Figure 1: Titration Model Characterization

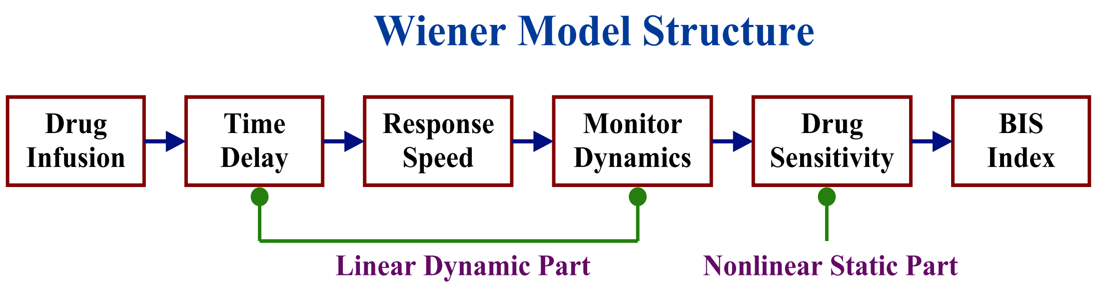

Figure 2: Titration Model Structure

times, two at the initial surgical preparation and one near incision. Analysis shows that the impact of Fentanal on the BIS values is minimal. As a result, it is treated as a disturbance and not explicitly modeled in this example. The drug infusion was controlled manually by an experienced anesthesiologist. The trajectories of titration (in μg/sec) and bolus injection (converted to μg/sec) during the entire surgical procedure were recorded, which are shown together with the corresponding BIS values in Figure 3.

The patient was given bolus injection twice to induce anesthesia, first at $t = 3$ minute with 20 mg and then at $t = 5$ minute with 20 mg. They are shown in the figure as 10000 μg/sec for two seconds, to be consistent with the titration units. The surgical procedures were manually recorded. Three major types of stimulation were identified: (1) During the initial drug administration (the first 6 minutes), due to

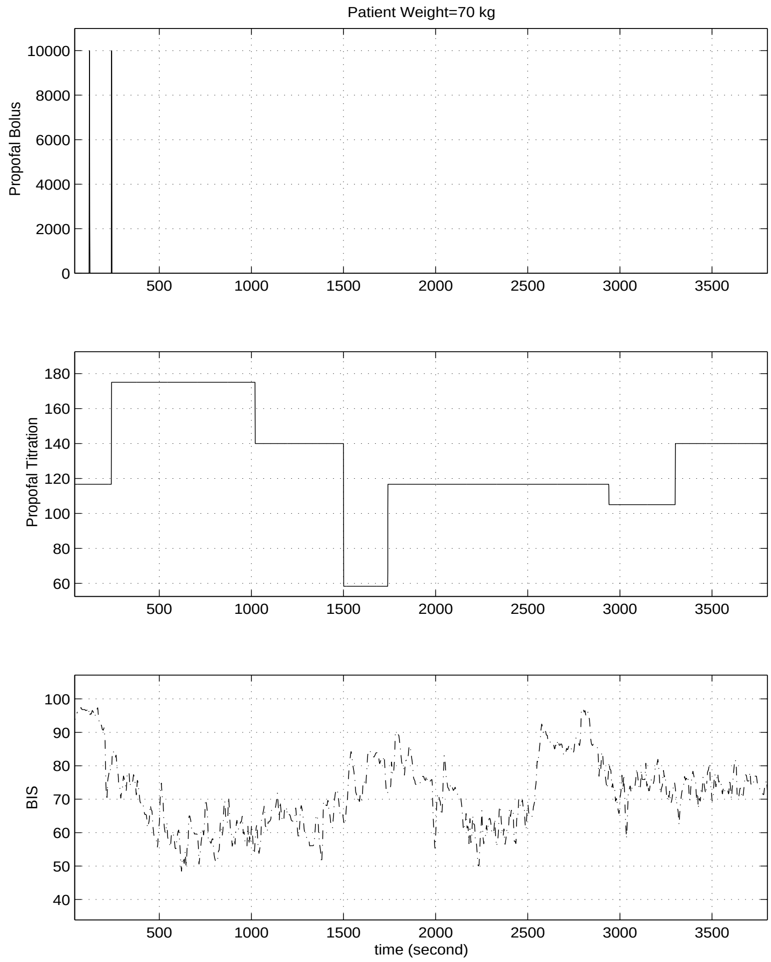

Figure 3: Actual Patient Responses

set-up stimulation and patient nervousness. (2) Incision at $t = 45$ minute for about 5 minutes duration. (3) Closing near the end of the surgery at $t = 60$ minute.

The data from the first 30 minutes are used to determine model parameters and function forms. The infusion pump model and the BIS monitor model can be derived or identified with limited impact from real data. For the systems used in this study, the time constant for the infusion pump model is estimated as $T_i = 0.5$ second. The delay time and time constant of the BIS monitor depend on the setting. For a short window selection (for fast response), these parameters are estimated as $\tau_b = 10$ second and $T_b = 10$ second.

For estimating the parameters in the patient block, the data in the interval where the bolus and stimulation impact is minimal (between $t = 10$ to $t = 30$ minutes) are used. By optimized data fitting (least-squares), we derive the estimated parameter values. The data-generated sensitivity function is shown in Figure 4.

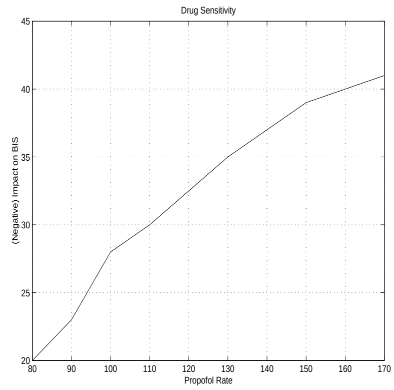

Figure 4: Drug Sensitivity Function (Titration)

The actual BIS response is then compared to the model response over the entire surgical procedure. Comparison results are demonstrated in Figure 5. Here, the inputs of titration and bolus are the recorded real-time data. The model output represents the patient response very well. In particular, the model captures the key trends and magnitudes of the BIS variations in the surgical procedure. This indicates that the model structure contains sufficient freedom in representing the main features of the patient response.

3 Parameterization and Identification Problems

For efficient identification of Wiener models, fast identification algorithms must be developed. Consider the Wiener system (1). One important observation is that since the nonlinear function represents the steady-state response of a given patient to the drug, it is always a strictly monotone function (the higher the drug infusion rate, the more the impact of the drug on the steady-state output). It will become clear that this property can be utilized to derive efficient identification algorithms for Wiener systems.

Suppose that $h(\cdot)$ in (1) is continuously differentiable and strictly monotone in the operating range Ω_x of x_k. For concreteness, assume that $0 < \underline{\beta} \leq \partial h/\partial x \leq \overline{\beta} < \infty, \forall x \in \Omega_x$. As a result, $h(\cdot)$ has an inverse $f(\cdot)$. It is easily verified that if $h(x_k) = ax_k$, then one of the parameters in $\overline{\theta}$ is redundant. Hence, assume that $\overline{\theta}$ is monic, namely, $\overline{\theta}(1) = 1$. Accordingly, we define $\phi_k^T = [u_{k-1}, \ldots, u_{k-n}]$ and $\theta^T = [\overline{\theta}(2), \ldots, \overline{\theta}(n+1)]$. The prior information on θ is that $\theta \in \Omega_\theta$, where Ω_θ is

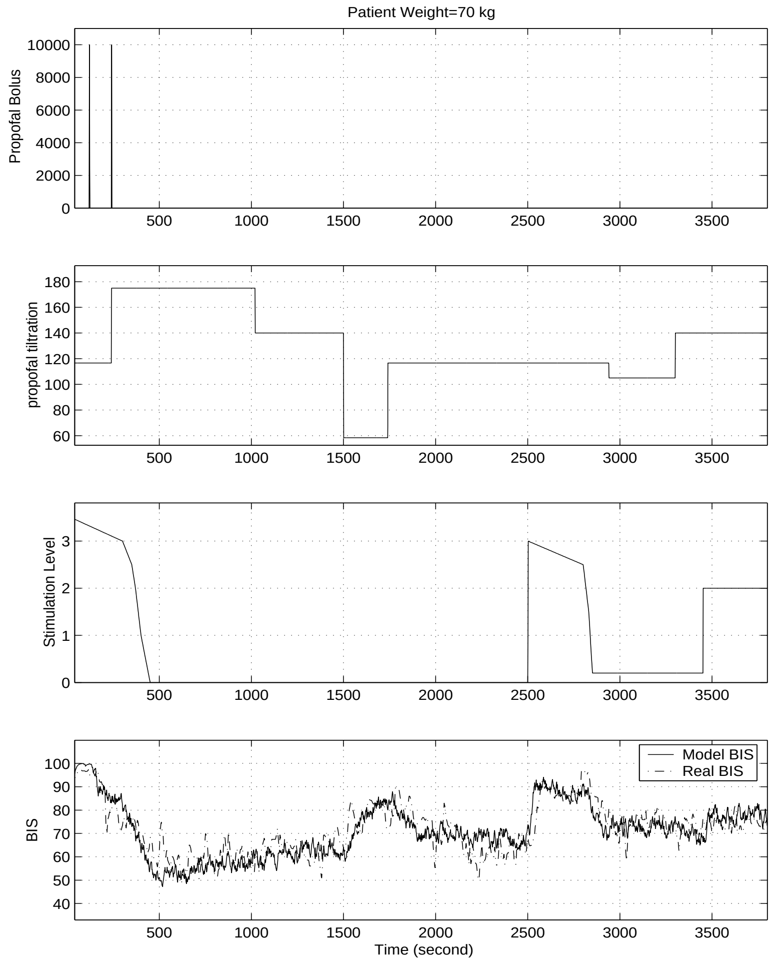

Figure 5: Patient Model Responses

convex and compact. Consequently, the system in (1) can be expressed as

$$\begin{cases} x_k = f(y_k) - w_k^0, \\ x_k = u_k + \phi_k^T \theta + \widetilde{\phi}_k^T \theta_u + v_k. \end{cases} \tag{2}$$

Observe that for any estimate $\widehat{f}(\cdot)$ of the function $f(\cdot)$, one can easily obtain the corresponding $\widehat{h}(\cdot)$ by numerically sampling the function $\widehat{f}(\cdot)$, inverting $\widehat{f}(\cdot)$ at the sampling points, and then using point interpolation to obtain $\widehat{h}(\cdot)$. As a result, this calculation will not be further discussed.

Now the problem is reduced to identification of $f(\cdot)$ and θ. Properties of identification algorithms depend on charcateristics of the disturbances, which will be discussed next.

3.1 Noise Characetrization

From $y_k = h(x_k) + \overline{w}_k$, we have

$$f(y_k) = f(h(x_k) + \overline{w}_k).$$

Since $f(\cdot)$ is the inverse of $h(\cdot)$, $f(h(x_k)) = x_k$ and

$$f(y_k) = x_k + f(h(x_k) + \overline{w}_k) - f(h(x_k)).$$

Hence, w_k^0 in (2) is in fact

$$w_k^0 = f(h(x_k) + \overline{w}_k) - f(h(x_k)).$$

Since $0 < \underline{\beta} \leq \partial h/\partial x \leq \overline{\beta} < \infty$, we have $0 < 1/\overline{\beta} \leq \partial f/\partial y \leq 1/\underline{\beta} < \infty$. By the mean value theorem $w_k^0 = (\partial f(z)/\partial y)\overline{w}_k$ for some z on the line segment joining $h(x_k)$ and $h(x_k) + \overline{w}_k$. Due to this dependence, w_k^0 may not be zero mean or identically distributed even if $\overline{w}_k$ is i.i.d. and zero mean. However, the following properties hold.

1. If $\{\overline{w}_k\}$ and $\{v_k\}$ are independent sequences, respectively, then $\{w_k^0\}$ is an independent sequence.

2. Let $\sigma_k^2 = E(w_k^0 - Ew_k^0)^2$. Then

$$|Ew_k^0| \leq \frac{1}{\underline{\beta}} E|\overline{w}_k|, \quad \sigma_k^2 \leq \frac{1}{\underline{\beta}^2} E(\overline{w}_k)^2, \quad \forall k.$$

Observe that if $\{\overline{w}_k\}$ is an i.i.d. sequence, then both $E|\overline{w}_k| = a$ and $E(\overline{w}_k)^2 = b$ are independent of k. Hence,

$$\sup_k |Ew_k^0| \leq \frac{a}{\underline{\beta}}, \quad \sup_k \sigma_k^2 \leq \frac{b}{\underline{\beta}^2}.$$

w_k^0 can be expressed as $w_k^0 = Ew_k^0 + w_k$ where Ew_k^0 can be viewed as a nonzero bias and $\{w_k\}$ is a sequence of zero mean independent (not necessarily identically distributed) random variables. Under this expression, (2) becomes

$$\begin{cases} x_k = f(y_k) - (Ew_k^0 + w_k), \\ x_k = u_k + \phi_k^T \theta + \widetilde{\phi}_k^T \theta_u + v_k. \end{cases} \tag{3}$$

3.2 Model Mismatch and Unmodeled Dynamics

Next, we introduce an approximate parametrization of $f(\cdot)$ by $f(\cdot,\alpha)$. The model class $\{f(\cdot,\alpha) : \alpha \in \Omega_\alpha\}$, where Ω_α is a compact set of parameter uncertainty, has the following properties: Let the output range be Ω_y. (1) $0 < \underline{\gamma} \le (\partial/\partial y) f(y,\alpha) \le \overline{\gamma} < \infty, \forall y \in \Omega_y, \alpha \in \Omega_\alpha$; (2) the gradient $g(y,\alpha) = (\partial/\partial\alpha) f(y,\alpha)$ is bounded by $|g(y,\alpha)| \le \gamma_g, \forall y \in \Omega_y, \alpha \in \Omega_\alpha$. The "true" parameter vector α is the optimal solution to

$$\delta = \min_{\alpha\in\Omega_\alpha} \max_{y\in\Omega_y} |f(y) - f(y,\alpha)|. \tag{4}$$

It follows that

$$\begin{cases} x_k = f(y_k,\alpha) - \Delta(y_k,\alpha) - (Ew_k^0 + w_k), \\ x_k = u_k + \phi_k^T\theta + \widetilde{\phi}_k^T\theta_u + v_k \end{cases} \tag{5}$$

where the model mismatch satisfies $|\Delta(y_k,\alpha)| \le \delta, \forall y_k \in \Omega_y, \alpha \in \Omega_\alpha$. Eliminating x_k, we arrive at

$$f(y_k,\alpha) - u_k = \phi_k^T\theta + \widetilde{\phi}_k^T\theta_u + \Delta(y_k,\alpha) + Ew_k^0 + w_k + v_k. \tag{6}$$

3.3 Identification Problems

It is noted that the uncertainty entries in (6) include a multiplicative term $\widetilde{\phi}_k^T\theta_u$ (proportional to the magnitude of u), an additive term $\Delta(y_k,\alpha_k) + Ew_k^0$ (uniformly bounded by $\delta + E|\overline{w}_k|/\underline{\beta}$), and a stochastic term $w_k + v_k$. For conciseness, we use the expression

$$f(y_k,\alpha) - u_k = \phi_k^T\theta + d_k + \delta_k + e_k \tag{7}$$

where the multiplicative uncertainty satisfies $|d_k| \le \varepsilon\|u\|_\infty$, the additive uncertainty due to parametrization is bounded by $|\delta_k| \le \delta$, and e_k is a stationary stochastic process with zero mean. Define the performance index as

$$J_k(\alpha,\theta) = \sum_{j=1}^{k} (f(y_j,\alpha) - u_j - \phi_j^T\theta)^2. \tag{8}$$

We seek $\begin{pmatrix}\alpha\\ \theta\end{pmatrix} \in \Omega \stackrel{\text{def}}{=} \Omega_\alpha \times \Omega_\theta \subseteq \mathbb{R}^{l_0+n}$ that minimizes $J_k(\alpha,\theta)$.

For a fixed $\alpha \in \Omega_\alpha$, disregard the constraint $\theta \in \Omega_\theta$ momentarily, we have the unconstrained least-squares estimator

$$\theta_{k+1}(\alpha) = \left(\sum_{j=1}^{k} \phi_k\phi_k^T\right)^{-1} \sum_{j=1}^{k} \phi_j[f(y_j,\alpha) - u_j]. \tag{9}$$

Since ϕ_k contains entries of u only, persistent excitation for identifying θ can be achieved by appropriate input design that is independent of α. If we consider

$J_k(\alpha) = \min_\theta J_k(\alpha, \theta)$, then minimizing $J_k(\alpha)$ with respect to α leads to another least-squares estimator. Such an approach may be viewed as an optimization procedure via repeated "marginal" optimization.

In lieu of this approach, we develop an identification algorithm by considering the optimization problem with both parameters θ and α jointly via a linear parametrization. Nonlinear parameterizations of $f(\cdot)$ will be discussed in Section 6. Hence, suppose

$$f(y_k, \alpha) = \sum_{j=1}^{l} b_j(y_k)\alpha_j = p_k^T \alpha.$$

where $b_j(y_k), j = 1, \ldots, l$ are nonlinear base functions, $p_k^T = [b_1(y_k), \cdots, b_l(y_k)]$, $\alpha = [\alpha_1, \cdots, \alpha_l]^T$. Define

$$\psi_k^T = [-p_k, \phi_k]^T, \quad \text{and} \quad \Theta = \begin{pmatrix} \alpha \\ \theta \end{pmatrix} \in \mathbb{R}^{l_0+n}. \tag{10}$$

In view of (7), by defining $\zeta_k = -u_k$ we can write

$$\zeta_k = \psi_k^T \Theta + d_k + \delta_k + e_k, \tag{11}$$

where d_k is the unmodeled dynamics, δ_k represents the model mismatch, and e_k is the noise process. The minimization of the objective function $J_k(\alpha, \theta)$ now can be described by that of

$$J_k(\Theta) = \sum_{j=1}^{k} (\zeta_j - \psi_j^T \Theta)^2.$$

4 Identification Algorithms

An unconstrained least squares solution is:

$$\Theta_{k+1} = (\sum_{j=1}^{k} \psi_k \psi_k^T)^{-1} \sum_{j=1}^{k} \psi_j \zeta_j. \tag{12}$$

This estimator can, in fact, be recursified (see [10]) as

$$\begin{cases} \Theta_{k+1} = \Theta_k + a_k \Psi_k \psi_k (\zeta_k - \psi_k^T \Theta_k), \\ \Psi_{k+1} = \Psi_k - a_k \Psi_k \psi_k \psi_k^T \Psi_k, \\ \Psi_{k+1} = (\sum_{j=1}^{k} \psi_j \psi_j^T)^{-1}, \ a_k = (1 + \psi_k^T \Psi_k \psi_k)^{-1}. \end{cases} \tag{13}$$

To incorporate the constraint into the algorithm, we rewrite it as

$$\begin{cases} \Theta_{k+1} = \Pi_\Omega[\Theta_k + a_k \Psi_k \psi_k (\zeta_k - \psi_k^T \Theta_k)], \\ \Psi_{k+1} = \Psi_k - a_k \Psi_k \psi_k \psi_k^T \Psi_k, \\ \Psi_{k+1} = (\sum_{j=1}^{k} \psi_j \psi_j^T)^{-1}, \ a_k = (1 + \psi_k^T \Psi_k \psi_k)^{-1}, \end{cases} \tag{14}$$

where $\Pi_\Omega(x)$ denotes the closest point in Ω to x and Ω is the constraint region $\Omega = \Omega_\alpha \times \Omega_\theta$. Thus, (14) indicates that we are using a projected form of the least squares algorithm.

In place of the least squares estimation algorithm, one may use adaptive filtering algorithms that have lower computational complexity. To this end, consider adaptive filtering algorithms with decreasing step sizes $\{\mu_k\}$

$$\Theta_{k+1} = \Pi_\Omega[\Theta_k + \mu_k \psi_k (\zeta_k - \psi_k^T \Theta_k)]. \tag{15}$$

The step size μ_k satisfies $\mu_k \geq 0$, $\mu_k \to 0$, and $\sum_k \mu_k = \infty$. Such adaptive filtering procedures belong to the category of stochastic approximation algorithms. For a most updated account on stochastic approximation algorithms, we refer the reader to [7, 31].

While the above algorithms are standard recursive identification algorithms, the joint appearance of stochastic noise, model mismatch, and unmodeled dynamics makes it more difficult to analyze error bounds, convergence, and rates of convergence. Such analysis will be detailed in the next sections.

5 Convergence and Rates of Convergence

In this section, we first study convergence of the algorithms. Then we remark on how rates of convergence of the recursive algorithms can be obtained. Our attention will be devoted to the constrained adaptive filtering algorithms (15) with decreasing step sizes $\{\mu_k\}$

$$\Theta_{k+1} = \Pi_\Omega[\Theta_k + \mu_k \psi_k (\zeta_k - \psi_k^T \Theta_k)].$$

Define $\widetilde{\zeta}_k = \psi_k^T \Theta + e_k$. By (11)

$$\zeta_k = \widetilde{\zeta}_k + d_k + \delta_k. \tag{16}$$

Introduction of $\widetilde{\zeta}_k$ allows us to separate the effects of noise and "bias" due to the unmodeled dynamics and model mismatch. Let $\mathcal{F}_k$ be the σ-algebra generated by $\{\widetilde{\zeta}_j, e_j : j < k\}$. Denote the conditional expectation with respect to $\mathcal{F}_k$ by $E_{\mathcal{F}_k}$.

To prove the convergence of the recursive algorithm (15), in lieu of considering the discrete iterates directly, we take a continuous-time interpolation and work with appropriate function spaces. To relate the discrete-time iterates and continuous-time systems, we introduce the notation

$$\begin{aligned} t_k &= \sum_{i=1}^{k-1} \mu_i, \\ m(t) &= \begin{cases} k, & 0 \le t_k \le t < t_{k+1}, \\ 0, & t < 0. \end{cases} \end{aligned} \tag{17}$$

The function $m(t)$ relates the continuous time t with the discrete time k. Subdivide the interval $[m(t_k+t), m(t_k+t+s)-1]$ as

$$m_0 \le m(t_k+t) \le m(k,1) \le m(k,2) \le \cdots \le m(t_k+t+s)-1. \tag{18}$$

In the above, the notation $m(k,l)$ denotes that the partition point is k dependent. In what follows, for simplicity, we simply write m_l in lieu of $m(k,l)$. Select a sequence $\eta_k > 0$ such that

$$\frac{1}{\eta_k} \sum_{i=m_l}^{m_{l+1}} \mu_i \to 1 \quad \text{as} \quad k \to \infty.$$

In fact, in accordance with the given step size μ_k, we can choose η_k so that $\sum_{i=m_l}^{m_{l+1}} \mu_i \sim \eta_k$ modulo an end value. We need the following conditions.

(A1) The constraint set Ω is connected and compact with a continuously differentiable outer normal and a piecewise smooth boundary. Set $C(\Theta)$ to be the linear span of the outer normal at $\Theta \in \Omega$.

(A2) $E|\psi_k|^{4+\gamma} < \infty$ and $E|\widetilde{\zeta}_k|^{4+\gamma} < \infty$ for some $\gamma > 0$. Suppose that

$$\begin{aligned} &\frac{1}{\eta_k} \sum_{j=m_l}^{m_{l+1}-1} \mu_j E_{\mathcal{F}_m} \psi_j \psi_j^T \to A \ \text{ in probability}, \\ &\frac{1}{\eta_k} \sum_{j=m_l}^{m_{l+1}-1} \mu_j E_{\mathcal{F}_m} \psi_j \widetilde{\zeta}_j \to B \ \text{ in probability}, \\ &\frac{1}{\eta_k} \sum_{j=m_l}^{m_{l+1}-1} \mu_j E_{\mathcal{F}_m} \psi_j d_j \to D \ \text{ in probability}, \\ &\frac{1}{\eta_k} \sum_{j=m_l}^{m_{l+1}-1} \mu_j E_{\mathcal{F}_m} \psi_j \delta_j \to \Delta \ \text{ in probability}. \end{aligned} \tag{19}$$

(A3) $A \in \mathbb{R}^{(n+l)\times(n+l)}$ is a positive definite matrix, and $D \in \mathbb{R}^{(n+l)\times 1}$ and $\Delta \in \mathbb{R}^{(n+l)\times 1}$ satisfy

$$|D| = O(\varepsilon \|u\|_\infty) \ \text{ and } \ |\Delta| = O(\delta). \tag{20}$$

Remark 1 We elaborate on the conditions briefly. (A1) covers a large class of constraint sets. For $\Theta \in \Omega^0$, the interior of Ω, $C(\Theta)$ contains only the zero element. For $\Theta \in \partial\Omega$, the boundary of Ω, $C(\Theta)$ is the convex cone generated by the outer normal at Θ at which Θ lies. This is the most general condition discussed in [7, Section 4.3]. For example, the set can be a hyperrectangle. It also covers the case that $\Omega = \{\Theta : q_i(\Theta) \le 0,\ i = 1, \ldots, n_1\}$, where $q_i(\cdot)$ are continuously differentiable real-valued functions whose gradient $q_{i,\Theta}(\Theta) \neq 0$ if $q_i(\Theta) = 0$.

The moment condition in (A2) implies that $\{|\psi_k|^4\}$ and $\{|\widetilde{\zeta}_k|^4\}$ are uniformly integrable. Such uniform integrability will enable us to obtain tightness of certain sequences. The averaging conditions (A2) are of law-of-large-numbers types in the weak sense. Note that we assume neither independence nor specific distribution of the sequences. Using $E_{\mathcal{F}_m}$ is much weaker than without such a conditioning. For example, if the random sequences are independent or uncorrelated and stationary, then before taking the arithmetic averaging, the noise has already been averaged out with $E_{\mathcal{F}_m}$ used. In terms of practical aspects, these conditions are satisfied if the nonlinearity and unmodeled dynamics are time invariant and the drug infusion rates approach constants.

(A3) is a condition concerning the uncertainty. The meaning of (20) is as usual: There is some $K > 0$ such that

$$|D| \le K\varepsilon\|u\|_\infty \ \text{ and } \ |\Delta| \le K\delta.$$

To some extent, this may be considered the size of the uncertainties in the limit due to unmodeled dynamics and model mismatch. If we view e_k as the noise in the algorithm, the condition on D and Δ may be regarded as the bounds of the "bias" in the limit. In what follows, we demonstrate that the noise can be averaged out, and the mean dynamics of the system can be brought out.

5.1 Convergence

Note that in (15), due to the projection operator,

$$\begin{aligned}\Theta_{k+1} &= \Pi_\Omega[\Theta_k + \mu_k\psi_k(\zeta_k - \psi_k^T\Theta_k)] \\ &= \Theta_k + \mu_k\psi_k[\widetilde{\zeta}_k - \psi_k^T\Theta_k + d_k + \delta_k] + \mu_k R_k,\end{aligned}$$

where

$$\mu_k R_k = \Theta_{k+1} - \Theta_k - \mu_k\psi_k[\widetilde{\zeta}_k - \psi_k^T\Theta_k + d_k + \delta_k]$$

is the vector that has the shortest Euclidean length needed to bring $\Theta_k + \mu_k\psi_k[\zeta_k - \psi_k^T\Theta_k]$ back to the constraint set Ω.

In view of (17), define the continuous-time interpolation

$$\Theta^0(t) = \Theta_k, \quad \text{for } t \in [t_k, t_{k+1}).$$

To bring the "tail" of the sequence to the foreground, define the shifted sequence

$$\Theta^k(t) = \Theta^0(t + t_k).$$

That is, $\Theta^0(t)$ is a piecewise constant interpolation of Θ_k, and $\Theta^k(t)$ is $\Theta^0(t)$ shiftd by t_k. Similarly, define

$$R^0(t) = 0 \ \text{ for } t \le 0, \ R^0(t) = \sum_{i=1}^{m(t)-1} \mu_i R_i, \quad \text{for } t \ge 0,$$

and

$$\begin{aligned} R^k(t) &= R^0(t + t_k) - R^0(t_k), \quad \text{for } t \ge 0, \\ R^k(t) &= -\sum_{i=m(t+t_k)}^{k-1} \mu_i R_i, \quad \text{for } \ t < 0. \end{aligned}$$

We will use weak convergence methods to establish the convergence of the sequence of interest. To proceed, let us recall the definition of weak convergence. Suppose that X_k and X are $\mathbb{R}^r$-valued random variables. X_k is said to converge weakly to X if for any bounded and continuous function $\widetilde{g}(\cdot)$,

$$E\widetilde{g}(X_k) \to E\widetilde{g}(X) \ \text{ as } \ k \to \infty;$$

$\{X_k\}$ is said to be tight if for each $\eta > 0$, there is a compact set K_η such that

$$P(X_k \in K_\eta) \ge 1 - \eta \ \text{ for all } \ k.$$

The above definitions extend to random variables in a metric space. The notion of weak convergence is a substantial generalization of convergence in distribution. On a complete separable metric space, tightness is equivalent to sequential compactness, which is known as Prohorov's Theorem. Due to this theorem, we can extract convergent subsequences once tightness is verified.

In what follows, we will work with a function space $D^{l_0+n}[0,\infty)$, the space of $\mathbb{R}^{l_0+n}$-valued functions that are right continuous and have left-hand limits, endowed with certain weak topology (the Skorohod topology). To carry out the weak convergence analysis, we use a martingale problem formulation, which to some extent is a weak-sense solution of a stochastic differential equation. For various notations and terms in weak convergence theory such as Skorohod topology, Skorohod representation etc. and their use in stochastic approximation, we refer to [7] and [31], and the references therein.

Theorem 1 *Assume that* (A1)–(A3) *hold and* (21) *has a unique solution for each initial condition. Then* $(\Theta^k(\cdot), R^k(\cdot))$ *converges weakly to* $(\Theta(\cdot), R(\cdot))$*, which is a solution of the projected ordinary differential equation* (*ODE*)

$$\frac{d\Theta(t)}{dt} = B - A\Theta(t) + D + \Delta + r(t), \quad r(t) \in -C(\Theta(t)), \tag{21}$$

and

$$R(t) = \int_0^t r(s)ds.$$

In addition, suppose that there is a unique stationary point $\Theta^* \in \Omega^0$ (*the interior of* Ω) *to the ODE* (21)*. Let* $T_k \to \infty$*. Then* $\Theta^k(T_k + \cdot)$ *converges in probability to* Θ^**.*

Remark 2 Note that interior to Ω, the dynamics of the trajectories of (21) are determined by the ODE

$$\dot{\Theta}(t) = B - A\Theta(t) + D + \Delta,$$

which is a linear ODE and hence has a unique solution for each initial condition. The stationary point of this ODE is precisely $\Theta^* = A^{-1}(B + D + \Delta)$.

Proof. The proof is divided into three steps. The first step demonstrates the tightness of $\{\Theta^k(\cdot), R^k(\cdot)\}$; the second step is on the characterization of the limit process; the third step proves the last assertion of the theorem. In fact, we mainly needs to verify the tightness. Once this is done, we can use the technique as in [7] for the characterization of the limit process.

Step 1: Owing to the projection, $\{\Theta_k\}$ is bounded uniformly. To proceed, we first show that $(\Theta^k(\cdot), R^k(\cdot))$ is tight. Then we characterize its limit. To prove the tightness, define

$$z_k = \psi_k(\widetilde{\zeta}_k - \psi_k^T \Theta_k + d_k + \delta_k),$$

and

$$Z^k(t) = \sum_{i=1}^{m(t_k+t)-1} \mu_k z_k.$$

Then for any $\eta > 0$, $t > 0$, and $0 < s \le \eta$,

$$\begin{aligned} &R\left|Z^k(t+s) - Z^k(t)\right|^2 \\ &= E\left|\sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i z_i\right|^2 \\ &= E\sum_{j=m(t_k+t)}^{m(t_k+t+s)-1}\sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i\mu_j E(\widetilde{\zeta}_i - \psi_i^T\Theta_i + d_i + \delta_i)(\widetilde{\zeta}_j - \psi_j^T\Theta_j + d_j + \delta_j)\psi_i^T\psi_j. \end{aligned}$$

We examine each of the terms above.

Since

$$\sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \le O(s) \le O(\eta),$$

by virtue of the boundedness of $\{\Theta_k\}$ owing to the projection algorithm,

$$\begin{aligned}
&\sum_{j=m(t_k+t)}^{m(t_k+t+s)-1} \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \mu_j E|\Theta_i^T \psi_i \psi_j^T \Theta_j \psi_i^T \psi_j| \\
&\le \sum_{j=m(t_k+t)}^{m(t_k+t+s)-1} \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \mu_j [E|\psi_i|^4 + E|\psi_j|^4] \\
&\le K \sum_{j=m(t_k+t)}^{m(t_k+t+s)-1} \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \mu_j \\
&\le K\eta^2.
\end{aligned} \tag{22}$$

The moment condition in (A2) also implies that

$$\begin{aligned}
&\sum_{j=m(t_k+t)}^{m(t_k+t+s)-1} \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \mu_j E|\widetilde{\zeta}_i \widetilde{\zeta}_j \psi_i^T \psi_j| \\
&\le K \sum_{j=m(t_k+t)}^{m(t_k+t+s)-1} \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \mu_j [E|\widetilde{\zeta}_i \psi_i|^2 + E|\widetilde{\zeta}_j \psi_j|^2] \\
&\le K \sum_{j=m(t_k+t)}^{m(t_k+t+s)-1} \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \mu_j [E|\widetilde{\zeta}_i|^4 + E|\widetilde{\zeta}_j|^4 + E|\psi_i|^4 + E|\psi_j|^4] \\
&\le K \sum_{j=m(t_k+t)}^{m(t_k+t+s)-1} \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \mu_j \\
&\le K\eta^2.
\end{aligned} \tag{23}$$

Similarly, the boundedness of $\{d_k\}$ and $\{\delta_k\}$ and the moment condition on $\{\psi_k\}$ imply that

$$\begin{aligned}
&\sum_{j=m(t_k+t)}^{m(t_k+t+s)-1} \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \mu_j E|\psi_i^T \psi_j (d_i + \delta_i)(d_j + \delta_j)| \\
&\le K\eta^2.
\end{aligned} \tag{24}$$

Combining (22)–(24),

$$\lim_{\eta \to 0} \limsup_{k \to 0} |Z^k(t+s) - Z^k(t)|^2 = 0. \tag{25}$$

As for the projection or reflection term,

$$|R^k(t+s) - R^k(t)| \le K \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i |\psi_i(\widetilde{\zeta}_i - \psi_i^T \Theta_i + d_i + \delta_i)|.$$

Thus

$$\lim_{\eta\to 0} \limsup_{k\to 0} |R^k(t+s) - R^k(t)|^2 = 0. \tag{26}$$

By (25) and (26),

$$\lim_{\eta\to 0} \limsup_{k\to 0} |\Theta^k(t+s) - \Theta^k(t)|^2 = 0.$$

The tightness criterion then implies that $\{\Theta^k(\cdot)\}$ is tight. In fact, what have been proved is that $\{\Theta^k(\cdot), R^k(\cdot)\}$ is tight.

Step 2: Since $\{\Theta^k(\cdot), R^k(\cdot)\}$ is tight, by Prohrov's theorem (see [7]), we can extract weakly convergent subsequences. Select such a subsequence. For notational simplicity, still denote it by $\{\Theta^k(\cdot), R^k(\cdot)\}$. By Skorohod representation (without changing notation), we may assume that $(\Theta^k(\cdot), R^k(\cdot)) \to (\Theta(\cdot), R(\cdot))$ with probability one (w.p.1) and the convergence is uniform on any bounded time intervals. We proceed to characterize the limit process. A pertinent way of handling the problem is to verify that $(\Theta(\cdot), R(\cdot))$ is a solution of a martingale problem with operator $\mathcal{L}$. Let $\widetilde{g}(\cdot)$ be a smooth real-valued function with compact support. We need to show that

$$\widetilde{g}(\Theta(t), R(t)) - \int_0^t \mathcal{L}\widetilde{g}(\Theta(s), R(s))ds$$

is a martingale where $\mathcal{L}$ is the operator of associated with the projected ODE (21). To this end, we need only show that for any positive integer ν, $t_j \le t$, and bounded and continuous function $H_j(\cdot)$ with $j \le \nu$,

$$E \prod_{j=1}^{\nu} H_j(\Theta(t_j), R(t_j)) \Big[\widetilde{g}(\Theta(t+s), R(t+s)) - \widetilde{g}(\Theta(t), R(t)) - \int_t^{t+s} \mathcal{L}\widetilde{g}(\Theta(\tau), R(\tau))d\tau\Big] = 0. \tag{27}$$

Since that weak convergence method for stochastic approximation algorithms has been studied in detail in [7], we will only provide a short outline below with the function $\widetilde{g}(\cdot)$ omitted. It is easily seen that

$$\begin{aligned}\Theta^k(t+s) - \Theta^k(t) = & \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \psi_i \widetilde{\zeta}_i - \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \psi_i \psi_i^T \Theta_i + \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \psi_i d_i \\ & + \sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i \psi_i \delta_i + R^k(t+s) - R^k(t).\end{aligned} \tag{28}$$

Using the partition (18), we study each of the terms in (28). By considering (27), it is clear that we can insert conditional expectation $E_{\mathcal{F}_t}$ due to the measurability. Thus, for the second term in (28),

$$
\begin{aligned}
&\sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i E_{\mathcal{F}_{m(t_k+t)}} \psi_i \psi_i^T \Theta_i \\
&= \sum_l \sum_{i=m_l}^{m_{l+1}-1} \mu_i E_{\mathcal{F}_{m(t_k+t)}} \psi_i \psi_i^T \Theta_i \\
&= \sum_l \sum_{i=m_l}^{m_{l+1}-1} \mu_i E_{\mathcal{F}_{m(t_k+t)}} \psi_i \psi_i^T \Theta_{m_l} + \varpi_k \\
&= \sum_l \eta_k \frac{1}{\eta_k} \sum_{i=m_l}^{m_{l+1}-1} \mu_i E_{\mathcal{F}_{m(t_k+t)}} A\Theta_{m_l} + \sum_l \eta_k \frac{1}{\eta_k} \sum_{i=m_l}^{m_{l+1}-1} \mu_i E_{\mathcal{F}_{m(t_k+t)}} [E_{\mathcal{F}_{m_l}} \psi_i \psi_i^T - A]\Theta_{m_l} + \varpi_k,
\end{aligned}
\tag{29}
$$

where $\varpi_k \to 0$ in probability as $k \to \infty$ and

$$
\frac{1}{\eta_k} \sum_{i=m_l}^{m_{l+1}-1} \mu_i E_{\mathcal{F}_{m(t_k+t)}} [E_{\mathcal{F}_{m_l}} \psi_i \psi_i^T - A]\Theta_{m_l} \to 0 \quad \text{as} \quad k \to \infty
$$

by virtue of (A2). Using the interpolation $\Theta^k(\cdot)$, the limit of (29) can be shown to be

$$
\sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i E_{\mathcal{F}_{m(t_k+t)}} \psi_i \psi_i^T \Theta_i \to \int_t^{t+s} A\Theta(\tau) d\tau \quad \text{as} \quad k \to \infty. \tag{30}
$$

Likewise, it can be shown that as $k \to \infty$,

$$
\begin{aligned}
&\sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i E_{\mathcal{F}_{m(t_k+t)}} \widetilde{\psi}_i \zeta_i \to B, \\
&\sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i E_{\mathcal{F}_{m(t_k+t)}} \psi_i d_i \to D, \\
&\sum_{i=m(t_k+t)}^{m(t_k+t+s)-1} \mu_i E_{\mathcal{F}_{m(t_k+t)}} \psi_i \delta_i \to \Delta, \\
&R^k(t+s) - R^k(t) \to \int_t^{t+s} r(\tau) d\tau.
\end{aligned}
\tag{31}
$$

Combining (30) and (31), the desired mean dynamics (21) is obtained.

Step 3: Assume $\Theta^* \in \Omega^0$. Then reflection term drops. Define $\widetilde{\Theta}^k(t) = \Theta^k(T_k + t)$ and consider $\{\widetilde{\Theta}^k(\cdot)\}$. The tightness and weak convergence of $\{\widetilde{\Theta}^k(\cdot)\}$ can be established as in the previous case. For any $T > 0$, extract a convergent subsequence of $(\widetilde{\Theta}^k(\cdot), \widetilde{\Theta}^k(\cdot - T))$ with limit $(\Theta(\cdot), \Theta_T(\cdot)))$. It is readily seen that $\Theta(0) = \Theta_T(T)$.

Due to the projection, $\{\Theta_T(0)\}$ is tight. Write (21) in its variational form with the reflection term dropped. Then we have

$$\Theta_T(T) = \exp(-AT)\Theta_T(0) + \Theta^* + \widetilde{\varpi}_T \to \Theta^* \quad \text{as} \quad T \to \infty$$

because $\exp(-AT) \to 0$ and

$$\widetilde{\varpi}_T \stackrel{\text{def}}{=} \int_T^\infty \exp(-At)(B + D + \Delta)dt \to 0 \quad \text{as} \quad T \to \infty.$$

The theorem is thus proved. □

Remark 3 Note that in view of the expression (21), $r(\cdot)$ is the term needed to keep $\Theta(\cdot)$ in Ω. The interested reader is referred to [7, Section 4.3] for further details.

The uniqueness assumption on the stationary point is guaranteed by choosing the projection bounds to be large enough. An argument using a form of the Kuhn-Tucker points and the ideas of active constraints to verify the assertion is in [6, Chapter 9]. When $\Theta \in \Omega^0$ the interior of Ω, $r = 0$. In the actual calculation using the recursive algorithm, if the iterates repeatedly hover the bounding surface, we would increase the size of the projection region.

Remark 4 If we consider an algorithm without projection

$$\check{\Theta}_{k+1} = \check{\Theta}_k + \mu_k \psi_k [\zeta_k - \psi_k^T \check{\Theta}_k]. \tag{32}$$

Define

$$D_{k|j} = \begin{cases} \prod_{i=j+1}^k (I - \mu_i A), & \text{if } j < k, \\ I, & \text{if } j = k. \end{cases}$$

Then

$$\check{\Theta}_{k+1} = D_{k|0}\check{\Theta}_1 + \sum_{j=1}^k D_{k|j}\mu_j(A - \psi_j\psi_j^T)\check{\Theta}_j + \sum_{j=1}^k \mu_j D_{k|j}\psi_j\zeta_j. \tag{33}$$

By Gronwall's inequality and the moment condition (A2), we can show that $E|\check{\Theta}_k|^2 < \infty$. Then using the tightness criterion, we can show the interpolated process for $\check{\Theta}_k$ is tight and derive the corresponding weak convergence.

5.2 Remark on Rate of Convergence

Let us consider (15), and assume $\Theta_k \to \Theta^*$ w.p.1 and $\Theta^* \in \Omega^0$. Thus effectively, the truncation or projection can be dropped in the rate of convergence analysis. In addition, let us assume that the uncertainties due to the unmodeled dynamics and model mismatch are missing. Then, the problem reduces to a standard stochastic approximation algorithm as consider in [7]. Define

$$\rho_k = \psi_k(\zeta_k - \psi_k^T \Theta^*), \quad \text{and} \quad V_k = \frac{\Theta_k - \Theta^*}{\sqrt{\mu}_k},$$

where ρ_k is regarded as "effective noise." Note now $\zeta_k = \widetilde{\zeta}_k$. Dropping the projection term and d_k and Δ_k, we proceed to obtain a distributional limit. The statement is in the following theorem. Its proof can be obtained as in [7, Chapter 10]. Define $v^k(\cdot)$ to be the piecewise constant interpolation and right shift by t_k of V_k.

Theorem 2 *Assume that* $\{V_k\}$ *is tight, that* (34) *has a unique solution* (*in the sense of in distribution*) *for each initial condition, and that*

$$\sum_{i=1}^{m(t_k+t)-1} \frac{1}{\sqrt{\mu}_k}\rho_k \text{ converges weakly to a Brownian motion,}$$

whose covariance is Σt. *Then* $v^k(\cdot)$ *converges weakly to* $v(\cdot)$, *the solution of*

$$dv = -Avdt + \Sigma^{1/2}dw, \tag{34}$$

where $w(\cdot)$ *is a standard Brownian motion and* $\Sigma^{1/2}(\Sigma^{1/2})^T = \Sigma$.

The tightness of $\{V_k\}$ can be proved via a perturbed Liapunov function argument; see [7, Chapter 10]. By Theorem 2, the scaling $\sqrt{\mu}_k$ together with the stationary covariance of the diffusion given in (34), namely, S the solution of the Liapunov equation $AS + SA = \Sigma$ gives us the desired rate of convergence. In view of Theorem 2, $(\Theta_k - \Theta^*)/\sqrt{\mu}_k$ converges in distribution to $N(0, S)$ a normal random variable with mean 0 and covariance S.

Remark 5 Theorem 2 is obtained under the conditions that the unmodeled dynamics and the model mismatch are missing. When taking these uncertainties into consideration, if we assume that they decay in certain rates with respect to k, then order of magnitude estimates of may be obtained similar to the approach of [8].

6 Some Further Remarks

In this section we discuss several variants of the above algorithms and different parametrizations of the nonlinear function.

Constant Step-size Algorithm. First, in lieu of a sequence of decreasing step sizes, we may consider constant step algorithms, which are known to have better tracking ability for sligh time varying parameter:

$$\Theta_{k+1} = \Pi_\Omega[\Theta_k + \mu\psi_k(\zeta_k - \psi_k^T\Theta_k)]. \tag{35}$$

Convergence and rate of convergence of this algorithm can be studied by using essentially the same techniques as in the decreasing step-size case.

Iterate Averaging. To further improve its efficiency, we may also consider the algorithm with iterate averaging

$$\begin{cases} \Theta_{k+1} = \Pi_\Omega[\Theta_k + \mu_k \psi_k(\zeta_k - \psi_k^T \Theta_k)], \quad \text{with} \;\; 1/k = o(\mu_k), \\ \overline{\Theta}_{k+1} = \overline{\Theta}_k - \dfrac{1}{k+1}\overline{\Theta}_k + \dfrac{1}{k+1}\Theta_{k+1}, \\ \overline{\Theta}_k \stackrel{\text{def}}{=} \dfrac{1}{k}\displaystyle\sum_{j=1}^{k} \Theta_j. \end{cases} \tag{36}$$

The weak convergence method can also be used to analyze algorithm with averaging (36). For this algorithm, the convergence of $\{\Theta_k\}$ follows from that of the argument as before, whereas the convergence of $\overline{\Theta}_k$ is a consequence of a familiar fact in analysis.

Recursive Least Squares. In (14), a recursive least squares algorithm is given. We comment on how such an algorithm can be studied by means of stochastic approximation algorithms. Note that under the averaging condition for $\{\psi_k \psi_k^T\}$ in (A2), we may write

$$\Psi_{k+1} = \frac{1}{k+1}\overline{\Psi}_{k+1} \;\; \text{with} \;\; \overline{\Psi}_{k+1} = \left(\frac{1}{k+1} \sum_{j=1}^{k} \psi_j \psi_j^T \right)^{-1}.$$

Note also the $\{a_k\}$ defined in (14) is a random sequence that takes positive values and that is bounded w.p.1. Define

$$\xi_k(\Theta_k, \psi_k, \zeta_k) = \overline{\Psi}_k \psi_k (\zeta_k - \psi_k^T \Theta_k),$$

and $\widetilde{\mu}_k = a_k/k$. Note that $\sum_k \widetilde{\mu}_k = \infty$ w.p.1. Thus the first equation in (14) can be rewritten as

$$\Theta_{k+1} = \Pi_\Omega[\Theta_k + \widetilde{\mu}_k \xi_k(\Theta_k, \psi_k, \zeta_k)], \tag{37}$$

which fits in the general algorithm with a sequence of time-varying functions $\xi_k(\cdot)$ and a sequence of random step sizes $\{\widetilde{\mu}_k\}$ considered in [7]. Thus we can proceed to modify the development in Section 4 of this paper to take into consideration of the uncertainties due to the unmodeled dynamics and model mismatch.

Nonlinear Parametrization of $f(\cdot)$. In certain applications (see Section 2), it may be desirable to employ certain model structures, retain physically-meaningful parameters, or reduce the number of parameters in parametrizing $f(y_k)$, making nonlinear parametrization a favored option. In this case, let $f(y_k, \beta)$, $\beta \in \Omega_\beta$ be the selected nonlinear parametrization. For system analysis and fast recursive algorithms, one can still use a linear parametrization $f(y_k, \alpha) = p_k^T \alpha$ as an algorithmic intermediate step.

The linear parameter α will be estimated from the above linear recursive algorithms. For a selected estimate $\widehat{\alpha}_k$, $\widehat{\beta}_k$ will be calculated by optimal curve fitting: Define

$$I_k(\beta, \alpha) = \frac{1}{2} \sum_{j=1}^{k} (f(y_j, \beta) - p_j^T \alpha)^2. \tag{38}$$

(Note that $f(\cdot)$ is a memoryless function. Hence, for a given α, this is a curve fitting problem.) Then, for a selected α we are seeking optimal $\widehat{\beta}$ that will minimize $I_k(\beta, \alpha)$

$$\eta_k(\alpha) = \min_{\beta \in \Omega_\beta} I_k(\beta, \alpha).$$

For computational simplicity, this will be recursified. Suppose

$$g(y_k, \beta) = \frac{\partial f(y_k, \beta)}{\partial \beta}.$$

Since

$$\begin{aligned} I_k(\beta, \alpha) &= \frac{1}{2} \sum_{j=1}^{k-1} (f(y_j, \beta) - p_j^T \alpha)^2 + \frac{1}{2} (f(y_k, \beta) - p_k^T \alpha)^2 \\ &= I_{k-1}(\beta, \alpha) + \frac{1}{2} (f(y_k, \beta) - p_k^T \alpha)^2 \end{aligned} \tag{39}$$

we have

$$\begin{aligned} G_k &:= \frac{\partial I_k(\beta, \alpha)}{\partial \beta} \\ &= G_{k-1} + g(y_k, \beta)(f(y_k, \beta) - p_k^T \alpha). \end{aligned} \tag{40}$$

Consequently, a natural recursified gradient updating algorithm is

$$G_{k+1} = G_k + g(y_{k+1}, \widehat{\beta}_k)(f(y_{k+1}, \widehat{\beta}_k) - p_{k+1}^T \widehat{\alpha}_{k+1}),$$

and the parameter updating is given by

$$\widehat{\beta}_k = \widehat{\beta}_{k-1} + \gamma_k G_k,$$

where γ_k is the step size that may vary with time. If the estimate $\widehat{\beta}_k$ is outside Ω_β, one can project it back into Ω_β: Let Π_β denote the projection operator on Ω_β. Then

$$\widehat{\beta}_k = \Pi_\beta[\widehat{\beta}_{k-1} + \gamma_k G_k].$$

Together with the linear estimation for α and θ, we have the following algorithms:

1. Initial Conditions: Select any $\widehat{\alpha}_0 \in \Omega_\alpha$, $\widehat{\theta}_0 \in \Omega_\theta$ (practically this can also be calculated by using a few initial data points), and $\widehat{\beta}_0 \in \Omega_\beta$. Also, V_0 is selected as a symmetric and positive definite matrix (practically this can also be calculated by using a few initial data points). G_0 is calculated from $\widehat{\alpha}_0$ and $\widehat{\beta}_0$ by $G_0 = g(y_0, \widehat{\beta}_0)(f(y_0, \widehat{\beta}_0) - p_0^T \widehat{\alpha}_0)$ after measuring y_0. $\widehat{\Theta}_0 = [\widehat{\alpha}_0^T, \widehat{\theta}_0^T]^T$.

2. Recursion: The matrices and vectors are updated in the following sequence: form ξ_k, p_k from the observations u_k, y_k, $k = 0, 1, \ldots$, and update recursively

$$\begin{cases} K_k &= \dfrac{V_k \xi_k}{1 + \xi_k^T V_k \xi_k} \\ V_{k+1} &= (I - K_k \xi_k^T) V_k \\ \widehat{\Theta}_{k+1} &= \Pi[\widehat{\Theta}_k + K_k(u_k - \xi_k^T \widehat{\Theta}_k)] \\ G_{k+1} &= G_k + g(y_{k+1}, \widehat{\beta}_k)(f(y_{k+1}, \widehat{\beta}_k) - p_{k+1}^T \widehat{\alpha}_{k+1}) \\ \widehat{\beta}_{k+1} &= \Pi_\beta[\widehat{\beta}_k + \gamma_{k+1} G_{k+1}] \end{cases} \tag{41}$$

7 An Application Case Study

We now describe a case study that utilizes Wiener models in real-time identification of anesthesia patient models.

From the patient data illustrated in Figure 5, the titration model is first extracted by an off-line method. The method eliminates the impact of surgical stimulation and drug impact from bolus injection, and produces a BIS response of the drug (propofol) titration on the patient as shown in Figure 6. Note that since anesthesia drugs will lower the BIS values from 100 (wide awake), we will use $100 - BIS$ as the drug impact output in system identification.

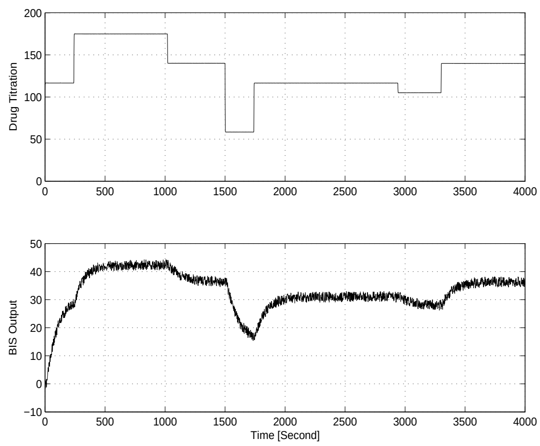

Figure 6: Patient BIS Response to Propofol Titration

Since actual model order and structures are unknown to the designer, we simply use either MA or ARMA models of various orders and evaluate their prediction capability. Different model orders will reflect variations in unmodeled dynamics. The total surgery lasted about 4000 seconds. We used the first 1000 data points for MA models. Then the prediction capability of the identified model is evaluated by applying it to the entire data.

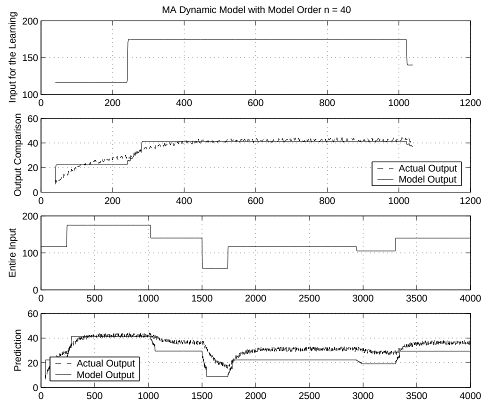

Figure 7: Moving Average Model of Order 40

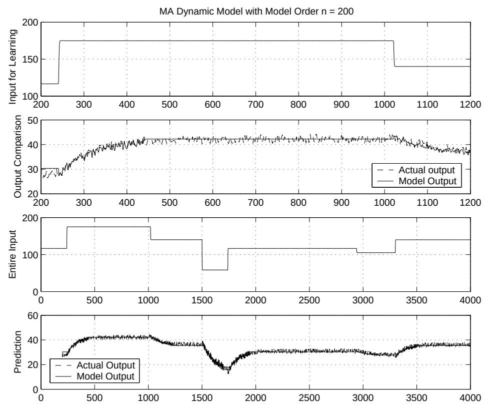

Figure 8: Moving Average Model of Order 200

8 Conclusions

Although Wiener/Hammerstein models have been used in a diversified array of practical systems, their applications to anesthesia patient dynamics are new and introduce some unique issues. These include nonlinear model structure selection, validation, parameter convergence, convergence rates, impact of model mismatch and unmodeled dynamics. This paper presents an effort to illuminate the relevance of these issues in this application and to study these issues rigorously in their mathematics foundations.

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