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Multivariable LPV control of anesthesia delivery during surgery

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Abstract— **In this paper, we present initial linear parameter-varying control efforts aimed at closed loop control of anesthesia delivery during surgery. The control designs are completed using a recent system identification based MIMO modeling framework for anesthetic pharmacodynamics.**

I. Introduction

Modeling and control of drug dosing in clinical pharmacology is particularly well-suited for applications of control design and analysis techniques. The increasing use of computers in the operating room combined with the ongoing development of non-invasive yet effective means of measuring a number of the goals of anesthesia, such as the *bispectral index* or BIS measure of sedation, real-time measurements of exhaled gas concentrations by spectroscopic methods, and the use of electromyographic methods to measure lack of movement, promise to make the incorporation of control techniques into the anesthetic delivery process imminent. In this paper, we discuss preliminary linear parameter-varying (LPV) based control efforts aimed at closed loop control of anesthesia delivery during surgery.

During surgery, the anesthesiologist continuously adjusts the delivery of anesthetic agents given to the patient to maintain a consistent and adequate level of *anesthetic depth*, that is, adequate levels of *hypnosis*, or lack of consciousness; *analgesia*, or lack of pain perception and the resulting autonomous system effects (e.g., increased heart rate and blood pressure); and muscle relaxation or lack of movement. Simultaneously, the anesthesiologist maintains ventilation parameters and monitors cardiovascular and respiratory functions such as heart rate (HR), blood pressure (BP), oxygen saturation and end-tidal (exhaled) carbon dioxide (CO_2) levels. Invasive montitoring is sometimes used to directly measure not only arterial blood pressure, but right-heart filling pressures (CVP), left-heart filling pressures (PCWP), and pulmonary arterial pressures. Cardiac output (CO) may be measured by thermodilation methods and then used to derive systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) and a host of other cardiac performance measures. Additionally, intra-operative blood samples are often taken and used to observe gas concentrations, blood-sugar levels, electrolyte concentrations and coagulation parameters.

The determination of when a patient is properly anesthetized thus is made by the anesthesiologist based on knowledge and experience of individual drug dose-response effects and synergistic effects of various drug combinations, combined with the observation of a number of indicators of patient status, such as those noted above. Vital signs and exhaled gases are commonly used to monitor patient status, but measurements of these quantities do not provide adequate information on the patient's anesthetic depth. At present, there does not exist a single widely accepted indicator for anesthetic adequacy, and in fact it is obvious that a single indicator will not suffice for describing adequate levels of the three main components of anesthesia. As a result, anesthesiologists perform the role of a multivariable feedback controller during surgery, observing multiple patient indicators while simultaneously adjusting and controlling dosing and delivery of a number of anesthetic agents as well as respiration system parameters.

Closed-loop administration of anesthetics during surgery could provide a number of benefits, such as tailoring and minimizing the overall amount of anesthetics required for individuals, and allowing the anesthesiologist to focus on critical safety tasks as necessitated by surgical demands on the patient and unexpected events. The main advantages of implementing closed-loop drug delivery would include reduced pharmaceutical costs, reduced recovery time, and improved long-term patient outcomes [1]. However, in order to design and implement feedback control schemes, mathematical models of the patient/drug delivery system are required.

The standard modeling paradigm that has been commonly used to describe the relationships between anesthetic inputs and patient output indicators (or effects) is that of *compartment models*. Pharmacokinetic (PK) compartment models are widely used as a means of predicting the disposition of drug in the body, by modeling the simultaneous diffusion of drug through body tissues and the flow of drug in blood. Most drugs are characterized by models containing a *central compartment*, which typically has a drug concentration corresponding to that of the blood, and peripheral compartments that represent groupings of internal organs and tissues of the body. As well, a theoretical *effect compartment* may be included which typically consists of a nonlinear pharmacodynamic (PD) model plus a first order linear time invariant system that is used to reflect the time-lag in the patient response to anesthesia. The resulting mathematical models are inherently single-input single-output (SISO) and consist of a system of ordinary differential equations plus a nonlinear function, representing the relations between the drug input function, the concentration of drug in the various compartments, and the effect of the drug on specific patient endpoints (see [2], [3], [4], [5] and the references therein for details). Unfortunately, as these models are strictly SISO, they are incapable of capturing the effects of disturbances, drug synergies, and the interrelation among effects in the human body.

Remark 1.1: Note that the PK-PD modeling framework offers just one approach to modeling drug response, and represents, essentially, a grey-box method for constructing SISO models.

In our research we have addressed this shortcoming directly by focusing on (1) the development of control-relevant mul-

tivariable models to describe patient response to anesthetic agents, ventilation controls and external stimuli [6], and (2) the development and implementation of MIMO control strategies for which patient safety and postoperative outcomes are improved. Although closed-loop control of anesthesia delivery has been studied for over 50 years [7], prior efforts have all essentially been SISO, thus, many important issues for MIMO modeling and control remain open. We have targeted some of these problems, on which we elaborate in the sequel. The remainder of this paper is organized as follows. In Section II, we present an overview of LPV control methods, and outline the MIMO switched-linear systems modeling approach we have introduced. Simulation results and comparisons from these modeling efforts are given. In Section III, we provide an overview of prior control efforts aimed at closed loop control of anesthesia delivery based on PK-PD models, followed by a discussion of our control design approach, including a discussion of the LPV models we have derived, the application of LPV synthesis techniques, and resulting control simulations. A discussion of future directions is given in Section IV.

II. Preliminaries

In this section we provide an overview discussion of LPV methods, and discuss our approach to modeling the response to anesthesia which relies on subspace identification methods.

A. Linear parameter-varying control methods

The study of LPV systems has been largely motivated by the gain-scheduling philosophy [8], [9]. The state-space entries of LPV systems are linear fractional functions of one or more exogenous parameters, which are assumed to vary with time. These time-varying parameters are assumed to be bounded, and in most cases, have bounded measurable time derivative. The trajectories of these time-varying parameters are *a priori* unknown other than the range of variations [10]. However, it is assumed these parameters may be measured or estimated upon operation of the system. The stability of the closed-loop system is guaranteed using constant quadratic Lyapunov functions [10], [11]. The following overview is excerpted from [10], [12].

Figure 1 shows the structure of the LPV control design paradigm. The upper two blocks in this figure, denoted M and Θ, represent a system whose dynamics are assumed to evolve relative to the set of time-varying parameters denoted by $\theta(t)$, as well as in time, that is, with state equations

$$x(t+1) = \tilde{A}(\theta(t))x(t) + \tilde{B}(\theta(t)) \begin{bmatrix} w(t) \\ u(t) \end{bmatrix} \quad (1)$$

$$\begin{bmatrix} z(t) \\ y(t) \end{bmatrix} = \tilde{C}(\theta(t))x(t) + \tilde{D}(\theta(t)) \begin{bmatrix} w(t) \\ u(t) \end{bmatrix}, \quad (2)$$

where $\tilde{A}(\cdot)$, $\tilde{B}(\cdot)$, $\tilde{C}(\cdot)$, $\tilde{D}(\cdot)$ are matrix-valued functions of appropriate dimensions, dependent on the vector-valued parameter function $\theta(t) = (\theta_1(t), \ldots, \theta_k(t))$. In the standard setup of [13], [10] we have that the parameter functions are known only to satisfy $-1 \leq \theta_i(t) \leq 1$, and that functions $\tilde{A}$, $\tilde{B}$, $\tilde{C}$, $\tilde{D}$ are linear fractional functions of the matrix $\Theta(t) = \text{diag}\left[\theta_1(t)I_{m_1}, \ldots, \theta_{p-1}(t)I_{m_{p-1}}\right]$, where the dimensions m_i are appropriately defined. The lower two blocks in this figure, denoted K and Θ_K, represent an $\mathcal{H}_\infty$ control synthesis constructed to satisfy stability and performance specifications over the range of variations assumed for the θ_i; such controllers also have dynamics that evolve with respect to the set of time-varying parameters $\theta(t)$, with state equations

$$x_K(t+1) = \tilde{A}_K(\theta(t))x_K(t) + \tilde{B}_K(\theta(t))u_K(t) \quad (3)$$

$$y_K(t) = \tilde{C}_K(\theta(t))x_K(t) + \tilde{D}_K(\theta(t))u_K(t), \quad (4)$$

where in feedback $y_K(t) = u(t)$ and $u_K(t) = y(t)$ from (1).

The resulting closed-loop transfer function from disturbance input $w(t)$ to controlled output $z(t)$ is denoted by

$$T(M, K, \Theta) = (\Theta \star M) \star (K \star \Theta_K), \quad (5)$$

where for a general system realization $M = \begin{bmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{bmatrix}$ and $\Theta = diag[\delta_1(t)I_{n_1}, \ldots, \delta_p(t)I_{n_p}]$ we define

$$\Theta \star M = (M_{22} + M_{21}\Theta(I - M_{11}\Theta)^{-1}M_{12})$$
$$M \star \Theta = M_{11} + M_{12}\Theta(I - M_{22}\Theta)^{-1}M_{21}.$$

The state dimensions and the dimensions of $\Theta(t)$ for the plant and controller indicate the dimensions of the constant realization matrices associated with the respective mappings $\Theta \star M$ and $K \star \Theta$. These matrices are partitioned as

$$\begin{bmatrix} A & B \\ C & D \end{bmatrix} \text{ and } \begin{bmatrix} A_K & B_K \\ C_K & D_K \end{bmatrix}$$

with the dimensions of A being $n \times n$ and of A_K being $n_K \times n_K$, where $\sum_{i=1}^{p} n_i = n$ and $\sum_{i=1}^{p} n_{Ki} = n_K$. The LPV H_∞ problem is formulated as finding a realization $M_K = \begin{bmatrix} A_K & B_K \\ C_K & D_K \end{bmatrix}$ such that the resulting LPV controller satisfies

- the closed-loop system given by (5) is internally stable for all assumed parameter variations
- the induced L_2 norm of the operator $T(M, K, \Theta)$ satisfies

$$\max_{||\Theta|| \leq \frac{1}{\gamma}} ||T(M, K, \Theta)||_\infty < \gamma. \quad (6)$$

Controllers satisfying our design objectives are found by applying algorithms resulting directly from the following theorem.

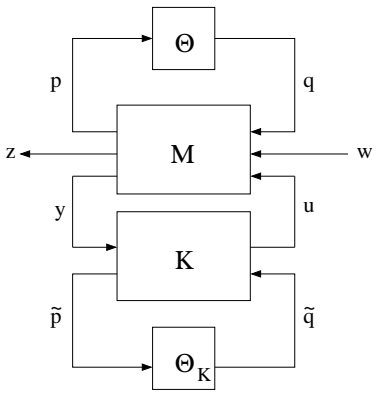

Fig. 1. Structure of LPV control

Theorem 2.1: [10], [12] Consider an LPV plant defined by (1) and shown by the interconnection of upper blocks of Figure 1, where M is a proper discrete-time plant with minimal realization

$$M(\lambda) = \left[\begin{array}{cc} D_{11} & D_{12} \\ D_{21} & D_{22} \end{array}\right] + \left[\begin{array}{c} C_1 \\ C_2 \end{array}\right] (\lambda I - A)^{-1} \left[\begin{array}{cc} B_1 & B_2 \end{array}\right],$$

Θ is the parameter operator given by $\Theta = diag[\delta_1(t)I_{n_1}, \ldots, \delta_p(t)I_{n_p}]$, and λ is the usual shift or delay operator. Let L_Θ denote the set of scaling matrices defined by

$$L_\Theta = \{L \text{ positive definite } : L\Theta = \Theta L, \|\Theta\| < \frac{1}{\gamma}\} \subset R^{n\times n}.$$

Assume

- (A, B_2, C_2) is stabilizable and detectable, and
- $D_{22} = 0$.

Let $\mathrm{Im}N_R = \mathrm{Ker}\left[\begin{array}{ccc} B_2^T & D_{12}^T & 0 \end{array}\right]$ and $\mathrm{Im}N_S = \mathrm{Ker}\left[\begin{array}{ccc} C_2 & D_{21} & 0 \end{array}\right]$. Then, the parameter-dependent H_∞ control synthesis is solvable if there exist pairs of symmetric matrices (R, S) in $R^{n\times n}$ and (L, J) in $R^{n\times n}$ such that

$$N_R^T \left[\begin{array}{ccc} ARA^T - R & ARC_1^T & B_1 \\ C_1RA^T & C_1RC_1^T - \gamma J & D_{11} \\ B_1^T & D_{11}^T & -\gamma L \end{array}\right] N_R < 0 \quad (7)$$

$$N_S^T \left[\begin{array}{ccc} ASA^T - S & A^TSB_1 & C_1^T \\ B_1^TSA & B_1^TSB_1 - \gamma L & D_{11}^T \\ C_1 & D_{11} & -\gamma J \end{array}\right] N_R < 0 \quad (8)$$

$$\left[\begin{array}{cc} R & I \\ I & S \end{array}\right] \geq 0 \text{ and } \left[\begin{array}{cc} L & I \\ I & J \end{array}\right] \geq 0 \quad (9)$$

Moreover, there exist γ-suboptimal controllers of order k if (7)-(9) hold for some (R, S, L, J) where R and S further satisfy

$$rank(I - RS) \leq k. \quad (10)$$

See [10] for a proof.

Equations (7)-(9) are LMIs that can be solved directly for (R, S, L, J) using public domain SDP solvers [14], [15]. Once solutions R and S are computed, an explicit controller is constructed by applying the synthesis algorithm given in [10], [12].

B. Multivariable switched-linear models

The modeling and control studies we have previously completed and published were based on data collected from a clinical study of 10 volunteers, completed under the supervision of Dr. Bloom []. In these studies we have found that the response of the patient (or volunteer in our case) transitions from one set of dynamic behaviors to another as the course of anesthesia takes the subject from the alert state to the sedated state. We therefore have proposed the use of linear switching systems, where the underlying subsystems are linear state-space models over which the volunteers' responses switch based on their sedative state. We briefly describe our data before discussing our methods and the simulation results we have obtained.

1) Clinical data: The original study was designed to define the relation between clinical evaluation of the state of conciousness, explicit recall, drug concentrations and BIS effects of the anesthetic agent isoflurane when administered alone to healthy volunteers under controlled conditions. Additionally, a series of external stimuli, or disturbances, were applied to the volunteers throughout the administration of anesthesia. These stimuli included: laryngeal mask insertion and removal, performed when the volunteer was considered completely sedated; evoked potential evaluations involving the application of short electrical stimulation signals to the wrist of the volunteer at a period of every 3 seconds and up to 100 μA and 100 V amplitude; and *alertness evaluations* which included yelling at, shaking, and squeezing the trapezius muscle of the volunteer. (See [16] for details of the clinical protocols).

Time-synchronized measured volunteer outputs included BIS levels, MAP and HR. Note that BIS values range from $0 - 100$, where a BIS value near 100 corresponds to a completely alert state, a BIS value around 60 corresponds to a moderate hypnotic state, a BIS value around 40 corresponds to a deep hypnotic state, and very low BIS values are referred to as characterizing a profound anesthetic state [17], [18]. For healthy individuals, normal ranges for MAP are between 70 and 110 mmHg, and the average resting HR for normal adults is around 70 beats per minute.

An example of a set of data taken from one subject during the study is shown in Figures 2 and 3. Note that we developed quantitative models of the stimuli applied to the volunteers during the study, hence in Figure 2 the plot with vertical axis labeled EP represents evoked potentials stimuli, that labeled LMA represents the laryngeal mask insertion process, and that labeled EVAL respresent the alertness evaluation tests. Similar quantitative models have been adopted in related studies [19], [20], [21]. The maximum amplitude of the external stimuli has been normalized to one. Note the distinct transitions, or the effective *switching* that has been attained between the BIS levels in the plot presented in Figure 3.

2) Switched-linear modeling via subspace identification: We have found that switched-linear models effectively capture the response to anesthesia. The constituent subsystems in the switched-linear models we have proposed have been constructed using subspace identification methods applied to the data described above. Specifically, we have implemented the N4SID algorithm, first introduced in [22], in MATLAB. (See [23], [24] for detaila on subspace identification methods). We have identified two linear state-space subsystems, denoted S_1 and S_2 and given by

$$\begin{array}{rcl} x^1(k+1) & = & A_1x^1(k) + B_1u(k) + w(k) \\ y(k) & = & C_1x^1(k) + D_1u(k) + v(k) \end{array}$$

and

$$\begin{array}{rcl} x^2(k+1) & = & A_2x^2(k) + B_2u(k) + w(k) \\ y(k) & = & C_2x^2(k) + D_2u(k) + v(k) \end{array}$$

which model the patient response in the awake and sedated states, respectively. In this framework, $u(k)$ and $y(k)$ represent the sampled input and output data described in the preceding section, $x(k)$ is the state vector, $w(k)$ and $v(k)$ are assumed to be white-noise processes, and A_i, B_i, C_i, and D_i, $i = 1, 2$,

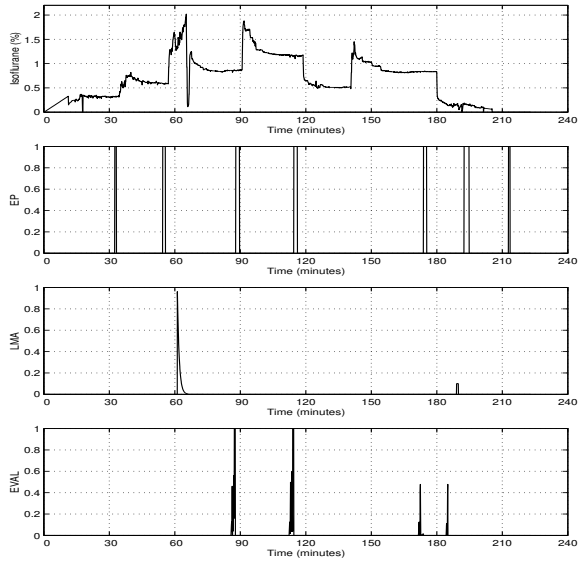

Fig. 2. Isoflurane and stimuli inputs versus time

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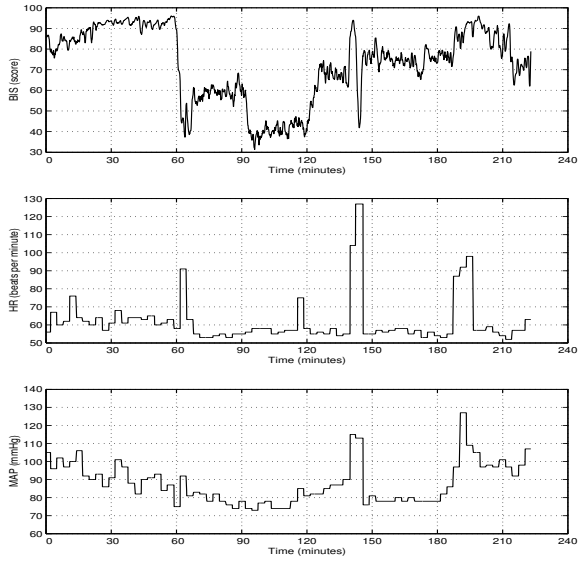

Fig. 3. BIS, HR and MAP outputs versus time

are constant real-valued matrices estimated by the subspace identification process.

Observed BIS values have been used to choose between one of two models for a patient's response to anesthesia and stimuli (i.e., the alert models, and the sedated models which include both moderate and deeply sedated states). Switching between these two models occurs based on a BIS threshold value of 70; this choice of switching value is physiologically motivated, as it was noted in [18] that approximately 50% of the population will be unconscious at a BIS value of 70. From the data we used, it is clear that this value always lies in the transition region from alert to sedate states. Upon switching from one subsystem, S_j, to the other subsystem, S_i the initial state for the subsystem S_i is calculated directly from the last output of S_j. Although the output will remain continuous, a jump in state values may result at the switching instant.

In order to complete a comparative analysis, we also modelled the dosing and related effects of isoflurane using the standard pharmacological approaches, i.e., PK-PD models. For the PK model, we used the mammillary compartment model identified by Yasuda, *et al* [25]; this model has been determined based on data collected from seven healthy male volunteers. An example of measured and predicted outputs for a switched-linear multi-input-to-BIS response model is shown for one volunteer in Figure 4, along with SISO (isoflurane-to-BIS) switched-linear and PK-PD responses. The thin solid line represents the measured data, and the thick solid line represents the simulated responses. Note the dashed verticle line in each of the plots; this line represents the point at which we separated the data record for estimation and validation purposes, for the switched-linear models. The entire data record is used to construct the PK-PD models. In summary, the switched-linear models we have introduced resulted in improved responses over the PK-PD models in comparisons of predictive capabilities, error signal means and variances over pooled data, normalized errors for individual patient data sets, and computational effort required. For further details regarding the switched-linear and PK-PD modeling efforts, complete estimation and prediction results, and quantitative comparisons of the modeling results, see [26], [6].

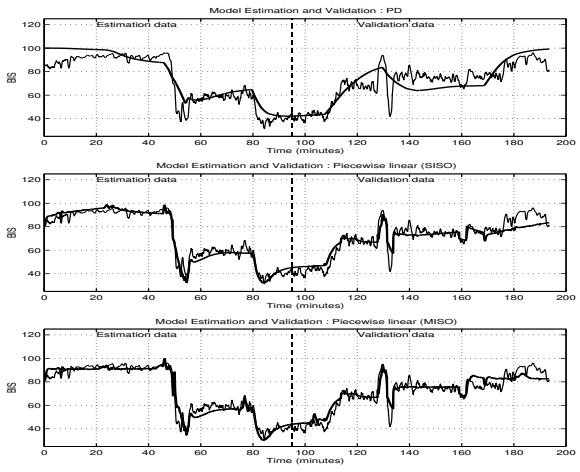

Fig. 4. Clinical data (thin line) and simulated responses (thick line) for Patient 1

Multi-input multi-output piecewise-linear models for MAP and HR responses also were constructed using the N4SID algorithm, from which a good fit was obtained. Representative examples of these model responses are shown in Figure 5.

We also have found that the switched-linear models for one individual provide reasonable *central* models, i.e., models applicable to a group of subjects, in the sense that simulated output responses obtained utilizing the input data set for one volunteer applied to the switched-linear model for another

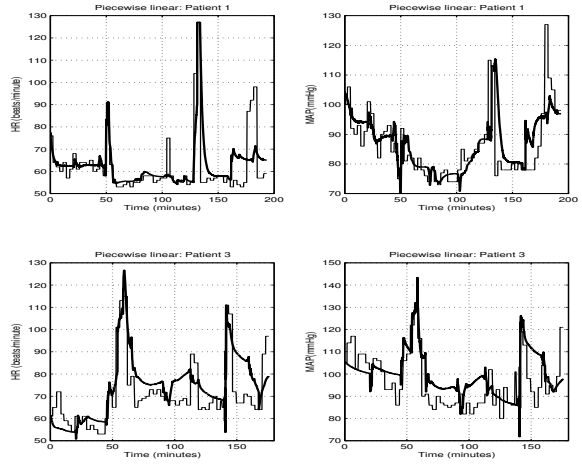

Fig. 5. Clinical data (thin line) and simulated responses (thick line) from switched-linear and PK-PD models for Patient 1 and Patient 3 HR and MAP responses

volunteer produces an acceptable fit to the output data for the first volunteer; see [26] for more details.

III. LPV MODELING AND CONTROL SYNTHESIS

Closed-loop control of anesthesia delivery previously has been considered in a number of studies. We outline a few of those studies here.

Schwilden and colleagues have used median frequencies from EEG power spectra as one measure of hypnotic effect to develop PK-PD model-based adaptive feedback control of propofol, methohexital, and alfentanil delivery during both clinical studies and for surgery [27], [28], [29]. A number of model-based closed-loop anesthesia control studies have been published by Gentilini and colleagues [30], [21], [31], [32], [33]. In [30], physiological models and rule-based controllers for the regulation of respiratory functions and MAP under administration of isoflurane are described; model predictive control is investigated in [21]; and control schemes for the regulation of MAP and sedation level using PK-PD models and loop-at-a-time control implementation for the anesthetic agent isoflurane are discussed in [31], [32]. Mortier had also earlier considered control of sedation level via BIS monitoring in [34], where PK-PD model-based adaptive control of propofol is implemented. More recently, Bailey *et al.* have completed adaptive and neural network based control designs for the regulation of unconciousness under administration of propofol [35]. Although this by no means represents an exhaustive discussion of prior work on closed-loop control of anesthesia, it presents the work most closely related to ours. The main point to consider here is that all of the prior and ongoing work discussed above involves the use of SISO models, and SISO control design, for what is clearly a MIMO system. We now discuss the MIMO control efforts we have pursued to date.

The use of switched-linear models in our work has been based, intuitively, on the course that the patient response to anesthesia takes from the alert state to the sedated state. Switching is based directly on knowledge of BIS values. However, most current piecewise-linear synthesis strategies are based directly on *states*, i.e., on transitions from one partition in state space to another, and require either direct knowledge or estimation of both the current state and reasonable partitions of the state space. In the identification-based models we use, the states in our state-space models have no direct physical relevance, hence state-space partitions and transitions between such partitions are not practical to affect.

As an alternative, we consider the LPV methods outlined earlier, in which BIS is viewed as a measurable time-varying system parameter. The benefit of utilizing LPV models is that these models are able to capture the transition from alert to sedate and back in a continuous manner. In order to transform the switched-linear models into LPV models, a curve fitting process was applied using the system realizations obtained for the patients in the awake (A) and sedated (S) states. For example, for the multi-input to BIS output models the relationships

$$P_{BIS}\left\{\begin{array}{lcl} A(\delta) &=& \frac{\delta(\delta-1)}{2}A_A + \frac{\delta+1}{2}A_S \\ B(\delta) &=& \frac{\delta(\delta-1)}{2}B_A + \frac{\delta+1}{2}B_S \\ C(\delta) &=& \frac{\delta(\delta-1)}{2}C_A + \frac{\delta+1}{2}C_S \end{array}\right. \tag{11}$$

$$\text{where } \delta(t) \;=\; 1 - \frac{2}{1+\exp^{\eta*(70-BIS(t))}}, \tag{12}$$

were implemented. This choice of the function for $\delta(t)$ is based on the fact that a BIS value around 100 corresponds to a completely alert state and a BIS value around 40 corresponds to a deep hypnotic state. As a result, $\delta = -1$ represents patients being in a totally awake state. In contrast, $\delta = 1$ represents patients being in a deeply sedated state. The slope η was selected as 0.2, providing a "smooth piecewise-linear" type of response.

For the multi-input to MAP/HR output models, the LPV curve fitting equations are defined as

$$P_{MAP/HR}\left\{\begin{array}{lcl} A(\delta) &=& \frac{1-\delta}{2}A_A + \frac{1+\delta}{2}A_S \\ B(\delta) &=& \frac{1-\delta}{2}B_A + \frac{1+\delta}{2}B_S \\ C(\delta) &=& \frac{1-\delta}{2}C_A + \frac{1+\delta}{2}C_S \end{array}\right. \tag{13}$$

Note that the resulting LPV systems have fairly high dimensions, for example typical resulting dimensions are $n_1 = 35$ in the δ parameter and $n_2 = 4$ in the state. To facilitate control design, multidimensional model reduction methods were first applied to the LPV models, resulting in reduced dimensions on the order of $n_{r_1} = 15$ in the δ parameter and $n_{r_2} = 4$ in the state [36]. Model reduction errors are on the order of 5% or less.

3) Preliminary LPV control design results: Desired reference trajectories for patient BIS values were determined by the attending anesthesiologist. The control goals are to track the BIS reference signal, attenuate the effect of disturbances, and for obvious safety reasons, maintain the HR and MAP within prespecified bounds. At the same time, the overall consumption of anesthetics should be minimized; these goals lead to a multi-objective control problem. In this discussion, we focus on tracking of the BIS reference trajectory when subjected to external disturbances (i.e., external stimuli). LPV control

synthesis algorithms such as those proposed in [37], [10], [13], [38], [11] have been implemented in MATLAB.

Preliminary control designs have been completed for each individual data set using the LPV/LMI algorithms outlined in Section II. Figure 6 shows one example of the control simulation results for the BIS reference tracking; a second example is given in Figure 7. In these 2-by-1 plots the upper plot represents the desired BIS reference trajectory (thick line) and the control simulation output (thin line); the lower plot represents the isoflurane control input (thick line) (in %volume concentration) and the isoflurane measurements from the associated clinical trial (thin line).

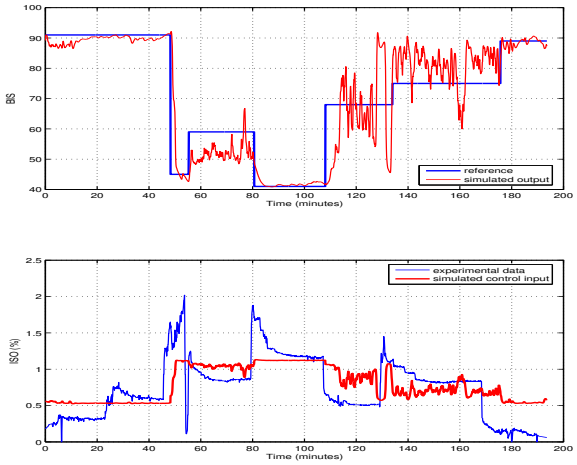

Fig. 6. Control simulation result of BIS reference tracking for volunteer 1

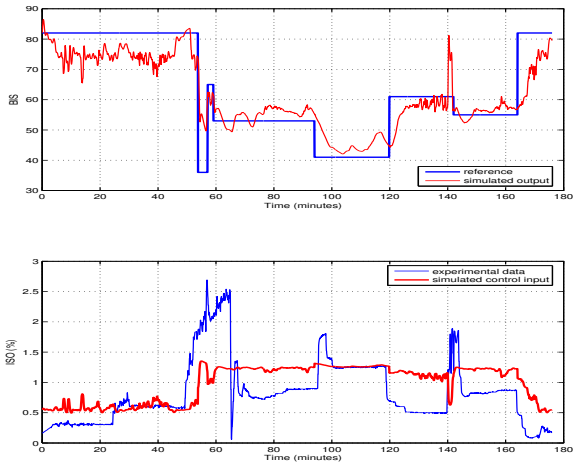

Fig. 7. Control simulation result of BIS reference tracking for volunteer 3

Controller cross-validations amongst patients for the BIS reference tracking also have been evaluated. Controllers generated from the estimated model for one subject have been implemented on other subjects' data and associated models. An example is shown in Figure 8. A number of such combinations have been evaluated; these results indicate that the controller generated for patient 1 can be used as a controller for patients 2 and 6 with little degradation in performance, and similarly the controller generated for patient 3 can be used as a controller for patients 5, 7, and 8 without experiencing degradation in performance. This suggests that the use of *central* models for population subgroups (which could be based on covariate analyses, for example) combined with robust control techniques is one multivariable approach that bears further investigation.

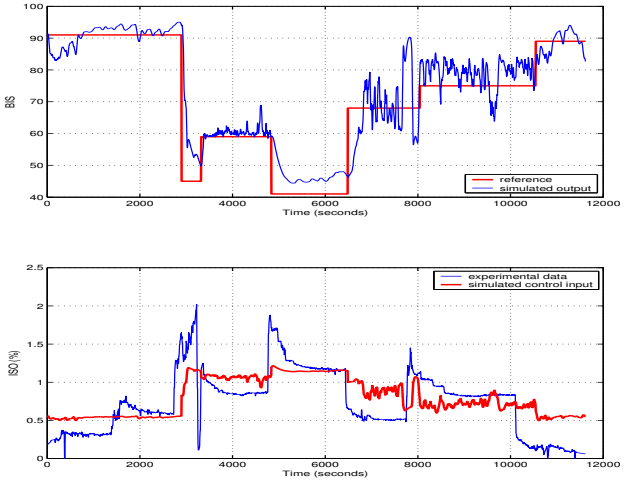

Fig. 8. Patient 3 controller with patient 1 model/data for BIS reference tracking

IV. Conclusions

We have discussed initial evaluation of the use of LPV control synthesis techniques for the problem of control of anesthesia delivery. The primary advantage of using the LPV control methodology at this time, versus direct switched-linear design methods, is the existence of synthesis algorithms and a priori provable performance guarantees. Ongoing efforts are aimed at improving and extending the control synthesis results discussed herein, the construction of multi-drug MIMO switched-linear models that incorporate multiple anesthetic agents, in particular models aimed at capturing the synergistic effects of combining opioid and hypnotic agents, and implementation of multi-objective control strategies (e.g., such as [39], [40]) aimed at optimizing dosing and administration of anesthetic agents affecting hypnosis and neuromuscular blockade levels while simultaneously regulating hemodynamic functions.

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