Design of $\mathcal{L}_1$ Adaptive Controllers for Human Patient Anesthesia

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Abstract

In this paper, the development and implementation of $\mathcal{L}_1$ adaptive control designs for anesthesia delivery to patients in surgical settings is presented. Our main objectives are the design of model-based feedback controllers ensuring that the patient's Bispectral Index profile tracks a prespecified reference trajectory, and demonstrates robustness to inter-patient variability. Patient models are constructed based on clinical trial data and gray box system identification methods. Controller switching mechanisms and specific safety measures are considered in the design and discussed in the paper. Simulation results are provided, demonstrating the effectiveness of the control methods.

Keywords: $\mathcal{L}_1$ Adaptive Control, Robust Adaptive Control, System

Identification, Output feedback, Anesthesia

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1. Introduction

During surgery, the main role of the attending anesthesiologist is that of a multivariable feedback controller for a complex and highly-coupled system. In this role, the anesthesiologist must continuously observe and adjust the rates and overall amounts of anesthetic agents delivered to the patient, with the fundamental goal being to maintain appropriate levels of sedation, analgesia and muscle relaxation. At the same time, the anesthesiologist determines appropriate ventilation parameters and monitors hemodynamic and respiratory functions, including heart rate, blood pressure, oxygen saturation and exhaled carbon dioxide (CO_2) levels. Our long-term goal in this research is to develop methods for *partially* automating the delivery of sedative anesthetic agents, allowing the anesthesiologist to focus on critical, or potentially urgent, events that occur during surgery.

The design and implementation of model-based feedback control in anesthesia delivery requires (1) adequate and appropriate means of sensing a patient's levels of sedation; and (2) relatively simple mathematical models capturing the patient response to anesthetic agents. Over the past two decades, the *bispectral index* (BIS), a statistical index based on phase and frequency relations between the component frequencies in EEG recordings, has been used extensively as a measure of sedation level (Glass et al. (1997); Sebel (1999); Avidan et al. (2008)).¹ The BIS value is a single dimensionless

¹There has been some controversy associated with this index (Lang (2013)), however the National Institute for Health and Care Excellence continues to recommend its use during application of intravenous anesthesia (Institute for Health & Clinical Excellence (2012)).

number ranging from 0 to 100, where 100 corresponds to a patient being fully awake and alert, and 0 corresponds to a silent EEG. A BIS value between 60 and 40 is considered a viable level for general anesthesia, in which the patient is not aware and surgery can be performed (Sebel et al. (1997)). In this paper, our main focus will be on the design and evaluation of feedback controllers that maintain an adequate *sedation level* yet require a minimum amount of anesthetic, and more importantly, that demonstrate robustness to some of the external disturbances encountered in a surgical setting. In particular, herein the focus is on designing and implementing novel $\mathcal{L}_1$ adaptive control techniques.

As with many pharmaceuticals and their intended effects, the BIS level response of a patient to the infusion and/or inspiration of anesthetic agents is typically nonlinear. In previous work it has been shown that patient response to anesthesia can be adequately captured by *multivariable piecewise-linear* models, with one linear model capturing patient response around an “awake” equilibrium state, and another linear model capturing patient response around a “sedated” equilibrium state (Lin et al. (2004); Beck et al. (2007)). These models incorporate external stimuli inputs and certain vital sign outputs. In this paper, a set of models is derived that corresponds to patient response to anesthesia in a “sedated” state, for six different patients’ sets of data. Using these models control synthesis and simulation results are presented, which are based on the $\mathcal{L}_1$ adaptive control methods of Hovakimyan & Cao (2010); these designs ensure stable performance in the presence of model uncertainties, achieve the desired BIS reference tracking objectives and are capable of rapid adaptation to variation in the system

47 model parameters.

48 This work is amongst the first applications of the $\mathcal{L}_1$ adaptive control
 49 methods to the anesthesia control problem (see also Ralph et al. (2011);
 50 Kharisov et al. (2012, 2013)). As compared to our previous work, in this
 51 paper an improved system identification (ID) process is presented, which re-
 52 sults in low-order patient models with reduced modeling errors, and several
 53 modifications to the $\mathcal{L}_1$ adaptive control architecture are proposed to ad-
 54 dress a variety of performance issues. Further, extended controller operation
 55 regimes are considered that incorporate switching and safety mechanisms.
 56 The resulting control architecture is shown to produce very small tracking
 57 error and to be robust with respect to the variability found across different
 58 patient responses to anesthesia. A preliminary version of some of the results
 59 presented in this paper can be also found in Kharisov et al. (2013); however
 60 this paper elaborates on the controller design algorithm, provides additional
 61 technical details on the controller architecture and system ID algorithm, and
 62 derives a stability proof of the $\mathcal{L}_1$ -adaptive controller in an open-loop regime.

63 The rest of the paper is organized as follows. To begin, a brief discussion
 64 of the construction of the models is given in Section 2. In Section 3, the
 65 $\mathcal{L}_1$ adaptive control architecture used is described. Simulation results are
 66 presented in Section 4. Finally, in Section 5, our results and ongoing research
 67 efforts are summarized.

68 **Notation:** The notation used in this paper is quite standard: $\mathbb{R}_0^+$ is used to
 69 denote the set of all nonnegative real numbers and $\mathbb{R}^+$ to denote the set of all
 70 positive real numbers; $\mathbb{I}$ denotes the identity matrix of compatible dimension.

71 The space of all bounded functions from $\mathbb{R}_0^+$ to $\mathbb{R}^n$ is defined as $\mathcal{L}_\infty$, and

the $\mathcal{L}_\infty$ -norm is defined by

$$\|\xi\|_{\mathcal{L}_\infty} \triangleq \max_{1 \leq i \leq n} \left\{ \sup_{\tau \geq 0} |\xi_i(\tau)| \right\} < \infty,$$

where the subscript i denotes the i^{th} component of $\xi \in \mathcal{L}_\infty$. The induced $\mathcal{L}_\infty$ -norm of a bounded-input and bounded-output (BIBO) stable proper system is defined by the $\mathcal{L}_1$ norm. For single-input, single-output (SISO) systems $G(s)$ the $\mathcal{L}_1$ norm is defined by

$$\|G(s)\|_{\mathcal{L}_1} \triangleq \int_0^\infty |g(t)| dt,$$

where $g(t)$ is the impulse response of $G(s)$. For a given m -input and l -output LTI system $G(s)$ with impulse response $\mathbf{g}(t) \in \mathbb{R}^{l \times m}$, the $\mathcal{L}_1$ norm is defined as

$$\|G(s)\|_{\mathcal{L}_1} \triangleq \max_{i=1, \dots, l} \left(\sum_{j=1}^m \|g_{ij}\|_{\mathcal{L}_1} \right),$$

where g_{ij} stands for ij^{th} element of the matrix $\mathbf{g}(t)$.

In addition, with a little abuse of notation, the notation of signals in the time or frequency domain is not distinguished, except by the argument.

2. Patient Modeling and System Identification

In the control design work discussed herein, clinical trial data used in earlier studies (Lin et al. (2004); Beck et al. (2007); Lin et al. (2008)) is referred to, which allows us to directly compare our control design results to previous controller results. The original clinical trial from which this data was collected was designed to define the relations between clinical evaluation of the state of consciousness, explicit recall, drug concentrations and BIS effects of the anesthetic agent isoflurane when administered to healthy

volunteers under controlled conditions. (Note: henceforth the volunteers will be referred to as *patients*.) In addition to the isoflurane, a series of external stimuli (i.e., disturbances) were applied to the patients throughout the administration of anesthesia. These stimuli included: laryngeal mask insertion and removal; evoked potential evaluations; and *alertness evaluations* that included yelling at, shaking, and squeezing the trapezius muscle of the patient. Time-synchronized output measurements of the patients' BIS as well as isoflurane concentrations were recorded every $\tau_p = 5$ seconds.

An example of a set of data taken from one subject during the clinical trial is shown in Figure 3. This data is fairly representative of the response expected from healthy volunteers to anesthesia and stimuli, however, as to be expected individual responses exhibit some variation. Inter-patient variability is one of the main motivations for considering the adaptive control techniques discussed in this paper.

As compared to our previous work in Ralph et al. (2011) and Kharisov et al. (2012), which employed black box system identification (ID), in this paper gray box system ID is used; that is, the model used has a specific LTI-based structure, with explicit parameters representing mean biases and an adaptive gain parameter capturing the time-varying nature of patient tolerance to the anesthetic agents. In Lin et al. (2004), it is shown that the patient dynamics in sedated state can be represented by an LTI model. To improve modeling errors, time varying gain is incorporated in the LTI model to account for changes in the patient sensitivity to the drug input during the

114 (trial) procedure, thus the model structure we consider is:

$$\begin{aligned} \dot{\mathbf{x}}_p(t) &= \mathbf{A}_p x_p(t) + \mathbf{b}_p(u(t) + \alpha_{in}), \quad \mathbf{x}_p(0) = \mathbf{x}_0, \\ y(t) &= k_a(t)(\mathbf{c}_p^\top \mathbf{x}_p(t) + \alpha_{out}) + \delta(t), \end{aligned} \quad (1)$$

115 where $u(t) \in \mathbb{R}$ and $y(t) \in \mathbb{R}$ are the control input (isoflurane concentra-
 116 tion) and the measured output (BIS index) respectively, ($\mathbf{A}_p \in \mathbb{R}^{n \times n}$, $\mathbf{b}_p \in$
 117 $\mathbb{R}$, $\mathbf{c}_p^\top \in \mathbb{R}^{1 \times n}$) are the realization matrices capturing patient dynamic re-
 118 sponse to anesthesia and disturbances, $\alpha_{in} \in \mathbb{R}$ and $\alpha_{out} \in \mathbb{R}$ are input and
 119 output mean biases, $k_a(t) \in \mathbb{R}$ is a time-varying output gain, and $\delta(t) \in \mathbb{R}$
 120 is an output disturbance. Closed-loop controllers are developed for the pa-
 121 tient sedated state, and therefore identification is completed using data only
 122 from intervals where BIS levels are below 70 (based on previously established
 123 BIS thresholds for patient transition from the alert to sedated state Sebel
 124 (1999)). For initial implementations of controllers discussed herein, the at-
 125 tending physician will perform the initial induction from the alert state to
 126 the lightly-sedated state in order to closely monitor initial patient response.
 127 Upon being lightly sedated and observed for safety reasons, the patient then
 128 will be switched to the proposed automated control regime.

129 The identification process herein is initiated by computing the gain $k_a(t)$.
 130 Since the sensitivity of the patient to the sedative gradually decreases dur-
 131 ing the surgery, piecewise linear functions are used to model the gain, which
 132 consists of 3 intervals: initial constant gain, adaptation interval, and final
 133 constant. Figure 1 shows a typical output gain $k_a(t)$ computed for Patient 1.
 134 This choice of model of $k_a(t)$ leads to four parameters that need to be iden-
 135 tified in order to completely define the function $k_a(t)$: initial gain, final gain
 136 and start and end times of gain rise. These parameters are determined by

137 averaging the BIS signal over two steady-state regions of the clinical data.
 138 For instance, Figure 3 shows three steady state regions at approximately
 139 $t = 4000$ s, $t = 6000$ s and $t = 10\,000$ s. For our design two of these regions
 140 were chosen: $t = 6000$ s and $t = 10\,000$ s, which result in the gain plot in Fig-
 141 ure 1. Note that the interval around $t = 4000$ s was not chosen because it is
 142 close to the initial sedation and hence potentially affected by the unmodeled
 143 sedation dynamics.

Figure 1: Output gain $k_a(t)$ for Patient 1.

144 The next step of the model (1) ID involves identification and removal of
 145 the input α_{in} and output α_{out} biases and gain normalization. The input and
 146 output biases are determined using the Matlab function *detrend*($\cdot, 0$), and the
 147 gain normalization is performed by dividing the clinical BIS response by the
 148 gain $k_a(t)$. The resulting data for Patient 1 are shown in Figure 2.

149 Inspection of the normalized data reveals intervals which contain small
 150 disturbances, show sufficiently rich dynamics and correspond to the sedated
 151 state. In Figure 2, these regions are colored in red. Note that time interval
 152 between 8100–8500s is avoided since it shows transients resulted from ex-
 153 ternal disturbance rather than model input (isoflurane). After the data for
 154 system ID is selected, system ID is then performed using subspace identifica-

Figure 2: Normalized data and ID intervals for Patient 1.

155 tion methods (Matlab function $n4sid(\cdot, n, \tau_p, 0)$), where appropriate candidate
 156 model orders are determined by evaluating system Hankel singular values.
 157 As compared to the results in Ralph et al. (2011) and Kharisov et al. (2012),
 158 where ID resulted in third and fourth order models, employing the approach
 159 described herein, namely incorporating the time-varying gain parameter $k_a(t)$
 160 explicitly into the modeling process, resulted in first and second order mod-
 161 els. The validation results for one of the patients' data sets is shown in
 162 Figure 3, showing that our model captures the patient transient and steady
 163 state behaviors during sedation.

164 Finally, an output disturbance model $\delta(t)$ is computed. For each patient
 165 the measured BIS signal is subtracted from the simulated response signal de-
 166 rived using the measured ISO as an input, as shown in Figure 3. The resulting
 167 disturbance for one of the patients is shown in Figure 4. This disturbance
 168 is used in our simulations to test the performance of the $\mathcal{L}_1$ adaptive con-
 169 trol system; in this setting the disturbance captures real measurement noise,
 170 response of the patient to the external stimuli and modeling errors. Al-

Figure 3: Model validation for Patient 1.

171 though the external stimuli applied to the patient in the clinical trial is more
 172 precisely described by an input disturbance model, the output disturbance
 173 model used here appropriately captures this disturbance signal via standard
 174 system-signal transformations (Åström & Murray (2010)).

 Figure 4: Output disturbance $\delta(t)$ for Patient 1.

175 To complete the simulations using the model given by (1), input and
 176 output sampling intervals of time τ_p are used, and an input saturation level
 177 of 3% concentration (by volume) of isoflurane. The block diagram of the
 178 complete patient model is shown in Figure 5. Our ID process is summarized
 179 in Table 1. Applying this process to all six patient data sets results in six

180 different models for which the $\mathcal{L}_1$ adaptive control design method is used,
 181 and model validation completed.

Figure 5: Block diagram of the patient model.

Step	Description	Matlab function
1	Analyze BIS response and compute gain $k_a(t)$. Normalize BIS using this output gain.	
2	Subtract mean biases α_{in} and α_{out} from the BIS data.	<i>detrend</i> ($\cdot$,0);
3	Determine data intervals that correspond to the sedated state, contain small disturbances, and contain sufficiently rich dynamics.	
4	Determine appropriate model order using Hankel singular value analysis.	<i>n4sid</i> ($\cdot$,1:11, τ_p ,0), <i>balreal</i> ($\cdot$, $\cdot$)
5	Perform system ID on preprocessed data from intervals determined in Step 3.	<i>n4sid</i> ($\cdot$, n , τ_p ,0);
6	Compute the output disturbance $\delta(t)$.	
7	Validate the ID model using clinical trial data.	

Table 1: System ID process.

182 3. The $\mathcal{L}_1$ Adaptive Controller Architecture

183 In this section the development of $\mathcal{L}_1$ adaptive controllers is reviewed,
184 which is aimed at controlling patient response to anesthesia via models con-
185 structed using the method as described in Section 2. The control objective
186 is to ensure that patient BIS levels track a desired reference trajectory with
187 guaranteed quantifiable performance bounds. The controller must simultane-
188 ously compensate for the variability inherent in patient response to anesthesia
189 and disturbances. The control signal is commanded concentration (measured
190 in % of volume concentration) of isoflurane in the inhaled gas mixture ad-
191 ministered to the patient, and the measured system output is the BIS index.

192 The $\mathcal{L}_1$ adaptive control framework provides numerous architectures that
193 offer solutions for a wide range of control system classes. In our case the
194 patient dynamics considered herein resulting from our system identification
195 process is given as a SISO transfer function, which implies that the output-
196 feedback $\mathcal{L}_1$ adaptive control architecture for non-strictly positive real (SPR)
197 systems is the most suitable (Cao & Hovakimyan (2009); Hovakimyan &
198 Cao (2010)). We note here that our focus is specifically on the use and
199 evaluation of $\mathcal{L}_1$ adaptive methods. However have been other robust and
200 adaptive techniques, providing for example fault tolerance to actuator faults
201 and allowing for system delays (Gayako & Yao (2011), Wu & Yang (2014)),
202 which will be considered in future designs.

203 In addition to developing a feedback control mechanism in this section,
204 the problem of safe controller switching is also considered. Since the patients'
205 models discussed in the preceding section are valid only during sedation (BIS
206 < 70), the designed controller would not be used to initiate the anesthetic

induction. Therefore due to safety considerations the surgery is initiated with manual (open-loop) control by the anesthesiologist, where the anesthesiologist directly sets desired concentrations of isoflurane. The $\mathcal{L}_1$ adaptive controller is engaged by a command from the anesthesiologist when the patient reaches an adequate sedated state, after which the anesthesiologist sets the desired value of BIS and the $\mathcal{L}_1$ adaptive controller then adjusts the concentration of isoflurane automatically. Note that the anesthesiologist should also have an opportunity to override the closed-loop control mechanism and return to an open-loop control regime at any time for safety considerations. The main requirement for the $\mathcal{L}_1$ adaptive controller during switching is to avoid undesired switching transients and bursting (Zaccarian & Teel (2002)).

Below, the main elements of the basic $\mathcal{L}_1$ adaptive control structure (Hovakimyan & Cao (2010)) are given and key theoretical results of $\mathcal{L}_1$ adaptive control theory reviewed. Then a switching scheme is introduced and the initialization method for $\mathcal{L}_1$ adaptive controllers, which avoids undesired switching transients, is discussed. Finally several modifications to the basic $\mathcal{L}_1$ adaptive control architecture are discussed, which allow us to address certain phenomena in patient dynamics and improve the closed-loop system performance.

3.1. $\mathcal{L}_1$ Adaptive Output-feedback Controller

The $\mathcal{L}_1$ adaptive output-feedback controller considers uncertain systems of the form:

$$y(s) = A(s)(u(s) + d(s)), \quad (2)$$

where $y(t) \in \mathbb{R}$ is the patient BIS value and $u(t) \in \mathbb{R}$ is the control input; in our case, this is percentage concentration, by volume, of the inhalational

231 sedative isoflurane. It is assumed that $A(s)$ is a strictly-proper unknown
 232 transfer function of unknown relative degree n_r , for which only a known
 233 lower bound $1 \leq d_r \leq n_r$ is available. This transfer function corresponds to
 234 the uncertain linear part of the patient dynamics, while $d(s)$ is the Laplace
 235 transform of the time-varying nonlinear uncertainty and disturbance $d(t) =$
 236 $f(t, y(t))$. The unknown function $f : \mathbb{R} \times \mathbb{R} \rightarrow \mathbb{R}$ is assumed to be Lipschitz,
 237 that is there exist constants $L \in \mathbb{R}^+$ and $L_0 \in \mathbb{R}^+$, such that

$$|f(t, y_1) - f(t, y_2)| \leq L|y_1 - y_2|, \quad |f(t, y)| \leq L|y| + L_0$$

238 hold uniformly in $t \geq 0$, where the values L and L_0 are assumed to be known.
 239 Note that the $d(t)$ term is meant to represent the stimuli terms in $\delta(t)$ as well
 240 as information about the time-varying gains and uncertainty in the system.

241 **Remark 1.** We note that although it is typically not possible to obtain exact
 242 expressions for the function $f(t, y)$ in order to compute precisely the values
 243 L and L_0 , conservative estimates for these values can be used to initiate the
 244 design.

245 The control objective is to design an adaptive output feedback controller
 246 such that the patients' BIS level $y(t)$ tracks the BIS reference input $r(t) \in \mathbb{R}$
 247 with transient and steady state control specifications given by the following
 248 *ideal* model:

$$y_{id}(s) = M(s)k_g r(s), \tag{3}$$

249 where $M(s)$ is a minimum-phase stable transfer function of relative degree
 250 d_r , and $k_g \in \mathbb{R}$ is a scaling factor, which results in tracking step reference
 251 commands with zero steady state error (see Section 2.1.2 of Hovakimyan

252 & Cao (2010)). Let $(\mathbf{A}_m \in \mathbb{R}^{n \times n}, \mathbf{b}_m \in \mathbb{R}^n, \mathbf{c}_m^\top \in \mathbb{R}^{1 \times n})$ be a minimal
 253 realization of the transfer function $M(s)$. Then the dc-gain of $M(s)$ is given
 254 by $\mathbf{c}_m^\top \mathbf{A}_m^{-1} \mathbf{b}_m$. Thus, the choice

$$k_g \triangleq \frac{-1}{\mathbf{c}_m^\top \mathbf{A}_m^{-1} \mathbf{b}_m}$$

255 ensures unit dc-gain of $M(s)k_g$ and hence zero steady state error $y_{\text{id}}(s) - r(s)$.

256 The $\mathcal{L}_1$ adaptive controller is comprised of the following elements (see
 257 Section 4.2 of Hovakimyan & Cao (2010)).

258 **Output Predictor:** The controller design relies on a *predicted* system re-
 259 sponse, which is based on the ideal system model $M(s)$ and an adaptation
 260 signal $\hat{\boldsymbol{\sigma}}(t)$, that is,

$$\begin{aligned}
 \dot{\hat{\mathbf{x}}}(t) &= \mathbf{A}_m \hat{\mathbf{x}}(t) + \mathbf{b}_m u(t) + \hat{\boldsymbol{\sigma}}(t), \quad \hat{\mathbf{x}}(0) = 0, \\
 \hat{y}(t) &= \mathbf{c}_m^\top \hat{\mathbf{x}}(t),
 \end{aligned} \tag{4}$$

261 where $\hat{\mathbf{x}}(t) \in \mathbb{R}^n$ and $\hat{y}(t) \in \mathbb{R}$ are the state and the output of the predictor
 262 respectively, and $\hat{\boldsymbol{\sigma}}(t) \in \mathbb{R}^n$ is a vector of adaptive parameters that are
 263 proportional to the output error $\hat{y}(t) - y(t)$ computed at fixed intervals of
 264 time. Note that while $d(s)$ in (2) is matched, the uncertainty estimation $\hat{\boldsymbol{\sigma}}(t)$
 265 in (4) is unmatched².

266 **Adaptation Laws:** Letting $\tilde{y}(t) \triangleq \hat{y}(t) - y(t)$, the piecewise-constant update
 267 law for $\hat{\boldsymbol{\sigma}}(t)$ is given by

$$\hat{\boldsymbol{\sigma}}(t) = -\boldsymbol{\Phi}^{-1}(T_s) \boldsymbol{\mu}(T_s) \tilde{y}(iT_s), \quad t \in [iT_s, (i+1)T_s), \quad i = 0, 1, 2, \dots, \tag{5}$$

²In adaptive control a term in the system state equation is called *matched* if it is in the span of the input matrix $\mathbf{b}_m$, that is if there exists some function $\xi(t) \in \mathbb{R}$ such that this term can be represented as $\mathbf{b}_m \xi(t)$. Similarly the term in the system state equation is called *unmatched* if it is not in the span of $\mathbf{b}_m$.

where T_s is an arbitrary positive constant, which can be associated with the sampling rate of the available CPU; $\Phi(T_s)$ and $\mu(T_s)$ are defined as

$$\begin{aligned}\Phi(T_s) &\triangleq \Lambda \mathbf{A}_m^{-1} (e^{\mathbf{A}_m T_s} - \mathbb{I}), \\ \mu(T_s) &\triangleq e^{\Lambda \mathbf{A}_m \Lambda^{-1} T_s} \mathbf{1}_1,\end{aligned}$$

where $\mathbf{1}_1 \triangleq [1, 0, \dots, 0]^\top \in \mathbb{R}^n$; and the state transformation matrix $\Lambda \in \mathbb{R}^{n \times n}$ is defined as

$$\Lambda \triangleq [\mathbf{c}_m, (\mathbf{D}\sqrt{\mathbf{P}})^\top]^\top.$$

In this definition $\mathbf{P} = \mathbf{P}^\top > 0$ is a solution to the algebraic Lyapunov equation

$$\mathbf{A}_m^\top \mathbf{P} + \mathbf{P} \mathbf{A}_m = -\mathbf{Q}, \quad \text{for arbitrary } \mathbf{Q} = \mathbf{Q}^\top > 0,$$

and $\mathbf{D} \in \mathbb{R}^{n-1 \times n}$ contains the null-space of $\mathbf{c}_m^\top (\sqrt{\mathbf{P}})^{-1}$, that is

$$\mathbf{D}(\mathbf{c}_m^\top (\sqrt{\mathbf{P}})^{-1})^\top = 0.$$

Remark 2. Note that the adaptation law (5) forms a negative feedback loop for the output prediction error dynamics, and the choice of the vector $\Phi^{-1}(T_s)\mu(T_s)$ implements a deadbeat type control for the error dynamics with the sampling time T_s . This design allows for achieving arbitrarily small prediction errors subject only to the size of the sampling time T_s choice.

Control Law: To define the control law, a strictly proper stable lowpass filter $C(s)$ with relative degree of at least d_r is considered. The control law is given by:

$$u(s) = F(s)k_g r(s) - \frac{C(s)\mathbf{c}_m^\top (s\mathbb{I} - \mathbf{A}_m)^{-1}}{\mathbf{c}_m^\top (s\mathbb{I} - \mathbf{A}_m)^{-1} \mathbf{b}_m} \hat{\sigma}(s), \quad (6)$$

 Figure 6: Block diagram of the $\mathcal{L}_1$ adaptive control system.

283 where $F(s)$ is a stable transfer function, which pre-filters the reference com-
 284 mand to ensure smoothness of the control input, and the second term in
 285 the control law aims to compensate for the system uncertainty. The block
 286 diagram of the closed-loop $\mathcal{L}_1$ adaptive control system is given in Figure 6.

287 3.2. $\mathcal{L}_1$ Reference System and Performance Bounds

288 The design of the $\mathcal{L}_1$ adaptive controller is completed by considering the
 289 following $\mathcal{L}_1$ reference system:

$$y_{\text{rf}}(s) = M(s)(u_{\text{rf}}(s) + \sigma_{\text{rf}}(s)), \quad (7)$$

$$u_{\text{rf}}(s) = F(s)k_g r(s) - C(s)\sigma_{\text{rf}}(s), \quad (8)$$

290 where

$$\sigma_{\text{rf}}(s) = \frac{(A(s) - M(s))u_{\text{rf}}(s) + A(s)d_{\text{rf}}(s)}{M(s)}, \quad (9)$$

291 and $d_{\text{rf}}(t) \triangleq f(t, y_{\text{rf}}(t))$. Note that the $\mathcal{L}_1$ reference system *depends* on the
 292 uncertainties, which implies that this reference system cannot be used in

 Figure 7: Block diagram of the $\mathcal{L}_1$ reference system.

the controller implementation; it is used for analysis purposes. The block diagram of the $\mathcal{L}_1$ reference system is given in Figure 7.

Remark 3. Considering (7)-(8) along with (9), it can be seen that the $\mathcal{L}_1$ reference system compensates for the uncertainties and the difference between $A(s)$ and $M(s)$ within the bandwidth of the lowpass filter $C(s)$. When $C(s) \equiv 1$ and $F(s) \equiv 1$, by substituting (8) into (7) the $\mathcal{L}_1$ reference system becomes identical to the desired model (3).

Since the $\mathcal{L}_1$ reference system depends on the uncertainties, its stability cannot be assumed as given. Therefore the following sufficient $\mathcal{L}_1$ -norm condition for stability can be derived (Cao & Hovakimyan (2009); Hovakimyan & Cao (2010)):

$$\|G(s)\|_{\mathcal{L}_1} L < 1, \quad (10)$$

where

$$G(s) \triangleq H(s)(1 - C(s)),$$

$$H(s) \triangleq \frac{A(s)M(s)}{C(s)A(s) + (1 - C(s))M(s)},$$

with $H(s)$ required to be stable. Since the transfer function $A(s)$ is not precisely known, the condition (10) needs to be satisfied for all systems $A(s) \in$

307 $\mathbb{A}$, where $\mathbb{A}$ denotes a known set of transfer functions from our conservative
 308 knowledge of the plant (2). This condition should be satisfied by a choice of
 309 the lowpass filter $C(s)$ and the desired model $M(s)$. Further details on the
 310 filter design for this $\mathcal{L}_1$ -norm condition can be found in Kim et al. (2011).

311 If the $\mathcal{L}_1$ -norm stability condition (10) holds, then the following perfor-
 312 mance bounds between the input and the output of the closed-loop adaptive
 313 system and the $\mathcal{L}_1$ reference system hold:

$$\|y_{\text{rf}} - y\|_{\mathcal{L}_\infty} \leq \gamma_1(T_s), \quad \|u_{\text{rf}} - u\|_{\mathcal{L}_\infty} \leq \gamma_2(T_s), \quad (11)$$

314 where $\gamma_1(T_s)$ and $\gamma_2(T_s)$ can be arbitrarily reduced by decreasing the sampling
 315 time T_s . For the equations of the bounds $\gamma_1(T_s)$ and $\gamma_2(T_s)$ as well as the
 316 stability proofs, the reader is referred to Section 4 of Hovakimyan & Cao
 317 (2010).

318 **Remark 4.** The tracking error between $y(t)$ and $y_{\text{rf}}(t)$, as well as the error
 319 between $u(t)$ and $u_{\text{rf}}(t)$, is uniformly bounded by a decreasing function of T_s .
 320 This implies that during the transient phase, one can make the response
 321 of the closed-loop adaptive system arbitrarily close to the response of the
 322 linear $\mathcal{L}_1$ reference system (7)-(8) by uniformly reducing T_s . The linearity of
 323 the reference system as well as its properties discussed in Remark 3 ensure
 324 predictable and guaranteed performance both during transient and steady
 325 state operation.

326 3.3. $\mathcal{L}_1$ Adaptive Controller Switching Logic

327 As noted in Hovakimyan & Cao (2010), a nonzero initialization error of
 328 the output predictor leads to exponentially decaying terms in the system

transient, which may lead to undesired behavior after the $\mathcal{L}_1$ adaptive controller is enabled. When using state-feedback architectures this problem can be resolved by proper initialization of the state-predictor using the first measurement of the system state; in the case of output-feedback this information is not available.

Therefore, in this paper the following switching method is proposed: the estimation loop of the $\mathcal{L}_1$ adaptive controller should be enabled at the initiation of the surgical procedure. However, while open-loop control is in place, the control signal generated by (6) (hereafter denoted $u_{\mathcal{L}_1}(t)$) is discarded and both the patient and the output-predictor are given control signals determined by the anesthesiologist, that is $u(t) = u_a(t)$. During this regime, the initialization transients in the estimation loop will converge and the prediction error will be reduced to its normal value. Once the anesthesiologist enables the closed-loop mode, the control input for both patient and output predictor is that generated by (6), that is $u(t) = u_{\mathcal{L}_1}(t)$. This eliminates bursting due to output predictor state mismatch. This scheme also allows switching back to open-loop mode if requested by the anesthesiologist. In order to avoid operator induced oscillations, re-enabling of the closed-loop mode is not allowed until a pre-specified dwell time $\tau_{dw} > 0$ has passed. A block diagram illustrating this switching scheme is shown in Figure 8.

The stability of this switching scheme, as well as associated performance guarantees, can be shown using a modification of the boundedness proof for the prediction error dynamics given in Hovakimyan & Cao (2010). Key steps of the proof for this switching scheme follow.

1. It is assumed that the open-loop control input $u_a(t)$ is bounded, that

is the anesthesiologist is able to perform adequate control. This fact along with the stability of the patient model yields bounded tracking during the open-loop regime.

2. Boundedness in the open-loop regime implies that uncertainty $\sigma(s)$ in (4.112) of Hovakimyan & Cao (2010) is bounded, and (4.112) holds. This allows us to follow the proof of Theorem 1 in Hovakimyan & Cao (2010) and conclude that $\|\tilde{y}_\tau\|_{\mathcal{L}_\infty} \leq \gamma_0(T_s)$ is bounded during the open-loop regime and the bound can be arbitrarily reduced. This insures stability of the $\mathcal{L}_1$ controller estimation loop during the open-loop operation.
3. After switching, the resulting closed-loop system is identical to that in Section 4.2 of Hovakimyan & Cao (2010) and hence all stability proofs hold.
4. The final step of the proof is to note that switching is performed by an external signal subject to a dwell time τ_{dw} , and thus it allows only for a finite number of switching events, which is sufficient for stability of the switched scheme (Liberzon (2003)), and the proof therefore completed.

3.4. Architecture Modifications for Improved Performance

Three modifications to the $\mathcal{L}_1$ adaptive control architecture are now incorporated, which improve performance of the closed-loop system. These modifications result in a novel $\mathcal{L}_1$ adaptive architecture for the application problem considered herein.

Hedging: The first modification is called *hedging* (Káráson & Annaswamy (1994)); for $\mathcal{L}_1$ adaptive control it was introduced in Li et al. (2009). The purpose of hedging is to improve stability and performance of the system in

the presence of an input saturation. This modification consists of adding a saturation block Δ_h with the same limits as the patient's input at the control input of the output predictor, which significantly reduces windup (Li et al. (2009)).

Output predictor modification: The second modification aims to reduce noise levels due to sampling of the patient's control signal. It consists of adding a sampler at the output-predictor's input with the same sampling period as the patient control signal τ_u . The modification relies on the decoupling property of $\mathcal{L}_1$ adaptive controllers, which is discussed in detail in Kharisov et al. (2011).

Filter with extended bandwidth: Finally, as was mentioned previously the $\mathcal{L}_1$ adaptive controller compensates for the disturbance within the low-pass filter bandwidth. This implies that a larger bandwidth will improve performance; however a larger bandwidth also reduces robustness of the closed-loop system (Hovakimyan & Cao (2010)). This creates a tradeoff between performance and robustness. In Figure 3 one can observe short intervals of time with severe disturbance, which corresponds to motion of the patients and external actions. Thus if a single lowpass filter is designed for the duration of the clinical procedure, this will achieve a conservative design, which will not compensate for disturbances during these short intervals of time. On the other hand if our filter addresses severe disturbances, the controller may exhibit weaker performance and higher noise amplification. Thus our approach is to design two separate filters: $C(s)$ for the main operation time, and a filter with extended bandwidth $C_e(s)$, which has improved performance for severe disturbances. Since such disturbances can be observed

Figure 8: Block diagram of the modified closed-loop $\mathcal{L}_1$ adaptive control system.

by the anesthesiologist (he/she observes visually when the patient is moving
and when surgical actions are applied), the anesthesiologist is allowed to de-
cide when to switch to the control law with the aggressive filter, and when
to switch back. The switching mechanism between the control laws as well
as the stability proofs are the same as described above for the $\mathcal{L}_1$ adaptive
controller. An illustration is given in Figure 8.

410 4. Controller Tuning and Simulation Results

In this section, simulation results are presented for the $\mathcal{L}_1$ adaptive controller defined in Section 3 and based on the 6 patient models derived as described in Section 2. The controller tuning procedure is first described and the controller parameters are provided, which are used in the simulations. Then, simulation results are given for two cases: (a) nominal patient models and (b) patient models with disturbances. In the second case simulation

417 results are compared to clinical data. To complete the control design per-
418 formance analysis, the total quantity of consumed isoflurane for each patient
419 is computed to verify that our $\mathcal{L}_1$ feedback control design does not lead to
420 increased consumption of the inhaled sedative.

421 *4.1. Tuning of the $\mathcal{L}_1$ Adaptive Controller Parameters*

422 The initial step in tuning of the $\mathcal{L}_1$ adaptive controller is the choice of
423 the output predictor. The output predictor specifies the desired transient
424 behavior of the closed-loop system (Hovakimyan & Cao (2010)). Since our
425 design objective is to achieve similar performance in terms of tracking and
426 disturbance rejection to that observed in the clinical trials, the desired system
427 is designed based on the characteristics of the transient response from clinical
428 trial results. It is also important to note that the time constants of the
429 output predictor should be chosen by considering the time constants of the
430 plant. For instance, if the settling time of the output predictor is chosen
431 to be much smaller (i.e., significantly faster) than the settling time of the
432 plant, this may lead to overly aggressive control action with large magnitude
433 input signals and unavoidable input saturation, causing the system to leave
434 the linear operation region. On the other hand, if the settling time of the
435 predictor is much larger than the settling time of the plant, this may result
436 in overly conservative design. The settling times for each patient model were
437 computed using standard Matlab routines, and were then used in the output
438 predictor design. Patient clinical BIS responses are shown in Figures 12-17;
439 the output predictor (desired) dynamics are set to

$$M(s) = -p_g \frac{0.01^2}{s^2 + 2 \cdot 0.9 \cdot 0.01s + 0.01^2}.$$

Figure 9: Comparison of the output predictor and clinical BIS transient responses.

440 This transfer function has a settling time of $\tau_s = 470$ s, which is slightly
 441 greater than the smallest settling time among all patient models. The model
 442 gain p_g is set to $p_g = 80$, which corresponds to the average gain of the patient
 443 models. Note that this gain plays an important role in ensuring satisfactory
 444 performance of the system. Figure 9 presents a comparison of the transient
 445 responses of patients 2 and 4 with $M(s)$ as given above.

446 Next, the lowpass filter $C(s)$ is designed. From the reference system (7)-
 447 (8), it can be seen that the $\mathcal{L}_1$ adaptive controller compensates for the uncer-
 448 tainty within the bandwidth of the lowpass filter $C(s)$. Therefore the choice
 449 of the filter bandwidth needs to ensure that the frequency range for the main
 450 disturbance content falls within the bandwidth of the filter $C(s)$. The power
 451 spectrum of the output disturbance $\delta(t)$ for all patients is considered, leading
 452 to the following second order filter choice:

$$C(s) = \left(\frac{0.02^2}{s^2 + 0.02s + 0.02^2} \right) \left(\frac{0.1}{s + 0.1} \right) \left(\frac{0.08}{s + 0.08} \right).$$

453 In Figure 10 the power spectrum of the disturbance $\delta(t)$ for all patient models
 454 and the gain plot of the filter $C(s)$ is shown for illustration. It can be seen

455 that the main frequency content of the disturbance is covered by the filter
 456 bandwidth, which leads to compensation of the majority of the disturbance
 457 effects on the system transient. Using the same approach, the second filter
 458 $C_e(s)$ is designed for operation under adverse conditions:

$$C_e(s) = \left(\frac{0.05^2}{s^2 + 0.05 \cdot 1.5s + 0.05^2} \right) \left(\frac{0.1}{s + 0.1} \right) \left(\frac{0.07}{s + 0.07} \right).$$

459 As can be seen in Figure 10 the bandwidth for $C_e(s)$ is larger than the
 460 bandwidth for $C(s)$, which results in better compensation for the disturbance.
 461 However, as mentioned before, $C_e(s)$ allows more high-frequency noise in the
 462 control channel as compared to the filter $C(s)$ and therefore should be enabled
 463 only in the presence of large disturbances.

(a) Disturbance power spectrum (b) Gain response of the lowpass filters in dB

Figure 10: Disturbance spectrum for all patient models and the lowpass filters gain response.

464 Since the patients' models constructed in Section 2 are adequate only
 465 during the patients' sedation ($\text{BIS} < 70$), the $\mathcal{L}_1$ adaptive controller is enabled
 466 after initial induction to the sedated state. While in practice this switching is
 467 done manually by the anesthesiologist, for our simulations using real clinical

data, a switching signal is defined for each patient data. The switching
 signal takes a 0 value before BIS falls below 70 and all initial transients are
 settled, and is equal to 1 subsequently. During the time interval for which
 the switching signal is 0, the actual clinical data are used for the control
 input of the patient model and the output predictor, which simulates the
 manual control mode of anesthesia. When the switching signal is changed
 to 1, the control signal generated by the $\mathcal{L}_1$ adaptive controller is used to
 provide tracking of the reference commands. This approach allows evaluating
 the behavior of the closed-loop control system in the presence of switching,
 along with the tracking performance of the $\mathcal{L}_1$ adaptive controller.

Similarly, the filter with extended bandwidth $C_e(s)$ is enabled by a com-
 mand from the anesthesiologist when he or she observes developing adverse
 conditions. In our simulations this command is considered an external signal
 to the feedback controller, which is defined separately for each patient model
 by inspection of the BIS clinical response. Figure 11 shows an example of
 one BIS clinical response. The areas with adverse disturbances are shown in
 cyan, and green intervals represent the command to enable $C_e(s)$.

Figure 11: Illustration of the choice of the switching intervals for the filter with extended bandwidth using Patient 6 clinical data.

485 In order to be able to compare the transient behavior of the $\mathcal{L}_1$ adaptive
486 controller with clinical data, the reference BIS command for each patient
487 model is based on inspection of the BIS clinical response, and estimation of
488 the target values for BIS as determined by the anesthesiologist.

489 Next the sampling time of the adaptation law is set to $T_s = 0.01$ s, which
490 is significantly faster than the time constants for the patient dynamics and
491 the output predictor. This choice leads to sufficiently small values of the per-
492 formance bounds (11). Further, set $\mathbf{Q} = \mathbb{I}$ and compute $\mathbf{D} = [0.9515 \ 0.3078]$.
493 The hedging saturation is set to $\Delta_h = 3$ % and the control signal sampling to
494 $\tau_u = 5$ s (this is the same as the patient model). The filter for the reference
495 commands is set to

$$F(s) = \frac{10}{s + 10}.$$

496 Note that since it is assumed that the patients' dynamics are uncertain,
497 in the above design only averaged and conservative information from the
498 models is used. Moreover, the controller parameters given above are used for
499 all simulations without any retuning.

500 4.2. Simulations for Nominal Patient Models

501 Simulations based on nominal patient models, that is without output dis-
502 turbances, are considered first. The simulation results for 6 patient models
503 are shown in Figures 12-17. For these simulations the lowpass filter with
504 extended bandwidth is not used, and the $\mathcal{L}_1$ adaptive feedback control is en-
505 abled at the beginning of the transient response. It can be seen that a *single*
506 $\mathcal{L}_1$ adaptive controller design achieves similar transient specifications during
507 control of the sedated state despite significant inter-patient model variabil-
508 ity. In fact, the transient specifications for all patient models are close to the

 Figure 12: $\mathcal{L}_1$ controller performance for Patient 1 without disturbances.

509 transient specifications of the response of the ideal system shown in Figure 9,
 510 which demonstrates the robustness of the $\mathcal{L}_1$ controller. Note that during
 511 some intervals, for example at $t = 5000$ s in Figure 17, the system output has
 512 significant undershoot, which occurs immediately after the patient reaches
 513 the sedated state and initial transients have not settled. This undershoot is
 514 due to the fact that the patient model, as well as the $\mathcal{L}_1$ adaptive controller,
 515 were tuned only for the sedated state *after the initial transients converge* and
 516 are not applicable for this time interval. This behavior illustrates the impor-
 517 tance of the initial manual anesthesia control and the associated switching
 518 scheme.

519 4.3. Simulations Using Clinical Trial Data

520 In this section, identified (uncertain) patient models *with* output distur-
 521 bances are considered. The simulation results for all six patients are shown
 522 in Figures 18-24. In these figures “Commanded BIS” stands for the ref-
 523 erence BIS command $r(t)$; “Clinical BIS” stands for the measured BIS re-
 524 sponse during clinical trials; “ $\mathcal{L}_1$ controller/nominal filter” is a modeled BIS

 Figure 13: $\mathcal{L}_1$ controller performance for Patient 2 without disturbances.

 Figure 14: $\mathcal{L}_1$ controller performance for Patient 3 without disturbances.

525 or Isoflurane input achieved by the $\mathcal{L}_1$ adaptive control system with nomi-
 526 nal filter $C(s)$ being used in control; “ $\mathcal{L}_1$ controller/extended filter” shows
 527 the portion of modeled BIS or Isoflurane input achieved by the $\mathcal{L}_1$ adaptive
 528 control system when the extended filter $C_e(s)$ was active. It can be seen
 529 that for all patients the achieved performance of the $\mathcal{L}_1$ adaptive controller
 530 is similar to the performance observed in the clinical data, that is with the
 531 anesthesiologist serving as the controller. The *single* $\mathcal{L}_1$ adaptive controller

 Figure 15: $\mathcal{L}_1$ controller performance for Patient 4 without disturbances.

 Figure 16: $\mathcal{L}_1$ controller performance for Patient 5 without disturbances.

532 demonstrates the ability to compensate for patient time-varying input gain
 533 and disturbances, as well as for inter-patient uncertainty. The noise level
 534 and the magnitudes of the generated control signal are comparable to the
 535 signals used in the clinical trials. Using the extended (more aggressive) low-
 536 pass filter reduced the tracking errors, as compared to the clinical results
 537 in the presence of adverse disturbances. However, comparing the results in
 538 Figure 18 to the simulations completed without use of the extended filter in

 Figure 17: $\mathcal{L}_1$ controller performance for Patient 6 without disturbances.

Figure 19, it can be seen that during the time intervals when the filter with
 extended bandwidth $C_e(s)$ is applied, the level of noise in the control signal
 is higher as compared to the results formed using the filter $C(s)$. This fact
 reflects a fundamental tradeoff between performance of the feedback system
 and its sensitivity to measurement noise. Since the control signal is sampled
 relatively slowly (5 s), the observed noise in the control signal does not cause
 issues for either the hardware or the patient, due to the large time scale. In
 this work, the extended filter with the noise level allowance is tuned to be
 approximately twice as large as the noise level for the nominal filter. Fi-
 nally, note that the proposed switching schemes, both for the filters and the
 $\mathcal{L}_1$ adaptive controllers, do not lead to any noticeable switching transients or
 “transfer bumps”.

4.4. Evaluation of Isoflurane Consumption

An important quantity to note in anesthesia is the overall amount of anes-
 thetic drugs consumed during surgery. There is a general tradeoff between
 achieved performance of the control system and the amount of the applied

 Figure 18: $\mathcal{L}_1$ controller performance for Patient 1.

 Figure 19: $\mathcal{L}_1$ controller performance for Patient 1 without use of the extended filter.

555 control input. The adaptive controller design discussed herein aimed to im-
 556 prove the control system performance and make it more predictable under
 557 significant uncertainty while maintaining the amount of anesthetic drug con-
 558 sumed, as compared to that used in the clinical trials. In Table 2 computed
 559 amounts of the consumed isoflurane (in liters) are compared during simula-
 560 tions and the clinical trials. It can be seen that, while there are no clear
 561 trends, the $\mathcal{L}_1$ adaptive feedback controller leads to similar consumption lev-

 Figure 20: $\mathcal{L}_1$ controller performance for Patient 2.

 Figure 21: $\mathcal{L}_1$ controller performance for Patient 3.

562 els of isoflurane as that resulting from manual control in the clinical trials;
 563 this validates our design against the clinical trial data.

564 5. Conclusions

565 In this paper, an application of $\mathcal{L}_1$ adaptive control techniques to the
 566 anesthesia control problem is presented. The system ID method described
 567 in this paper led to significantly reduced patient model orders as compared

 Figure 22: $\mathcal{L}_1$ controller performance for Patient 4.

 Figure 23: $\mathcal{L}_1$ controller performance for Patient 5.

568 to those in Kharisov et al. (2012), and the tracking performance and inter-
 569 patient robustness achieved with these control methods, in combination with
 570 comparable amounts of isoflurane used as compared to clinical data, are ex-
 571 tremely encouraging. Our initial results demonstrate the robustness of this
 572 control architecture; it remains to be determined what yields the best per-
 573 formance for the greatest number of patients. Data from additional surgical
 574 procedures will be used in future work to test this control approach un-

 Figure 24: $\mathcal{L}_1$ controller performance for Patient 6.

Patient	1	2	3	4	5	6
w/o disturbance, l	0.849	0.650	0.649	0.673	0.662	0.636
w disturbance, w/o $C_e(s)$, l	0.845	0.641	0.653	0.732	0.623	0.666
w disturbance, l	0.849	0.643	0.651	0.736	0.624	0.666
Clinical ISO, l	0.832	0.651	0.638	0.796	0.614	0.647

Table 2: Isoflurane consumption (liters).

575 der more typical surgical conditions, (i.e., with multiple anesthetic agents,
 576 disturbances, and actual surgical stimuli events). The control architecture
 577 presented in this paper explicitly takes into account that the anesthesiologist
 578 is a part of the control system. In particular, the presented design ensures
 579 safe switching between human-in-loop and closed-loop modes. We note that
 580 the performance guarantees of the $\mathcal{L}_1$ adaptive controller (given via com-
 581 putable performance bounds) can facilitate future studies in the direction of
 582 human factors and human-machine relations (Mort et al. (2005)).

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