Robust and Adaptive Control Methods for Patient Response to Anesthesia

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Acknowledgments:
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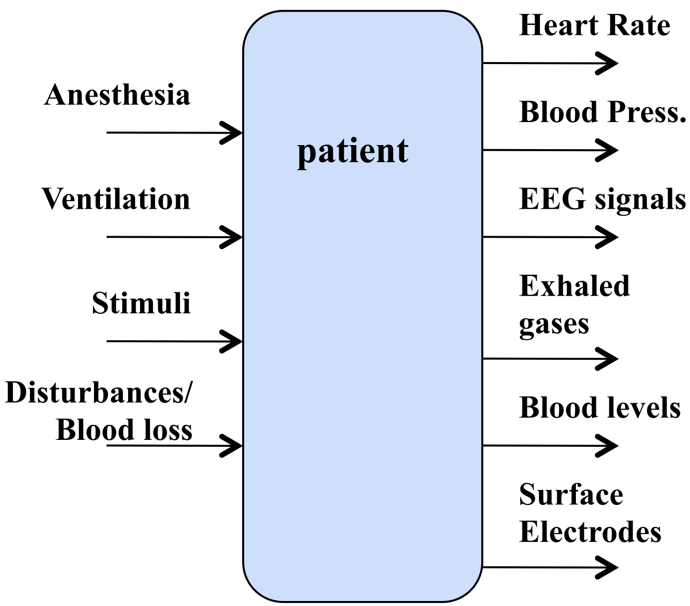
Outline

- **Introduction:** *the anesthesia control problem*
- **Modeling the Patient Response**
- **Robust and Adaptive Control Methods**
- **Control Simulation Results**

Problem Statement

Problem Statement

Anesthesia Control during Surgery



Anesthesiologist:

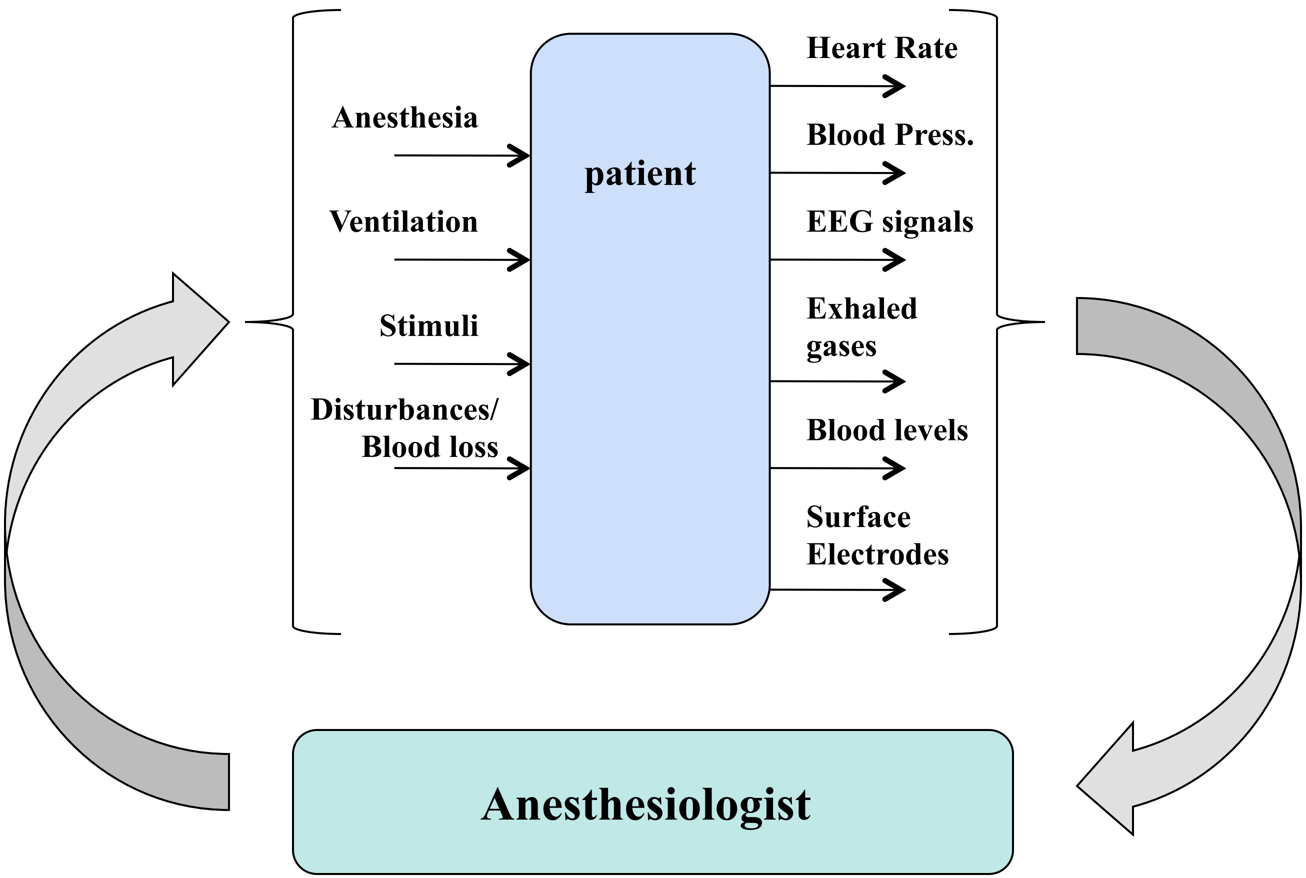
- Administers sedatives, analgesics, and neuromuscular blockades
- maintains ventilation parameters
- monitors cardiovascular and respiratory functions
- monitors blood chemistry:

blood-sugar levels, electrolyte concentrations, gas concentrations, coagulation parameters…

Goal: automate/optimize delivery and control of anesthesia

Problem Statement

Anesthesia Control during Surgery



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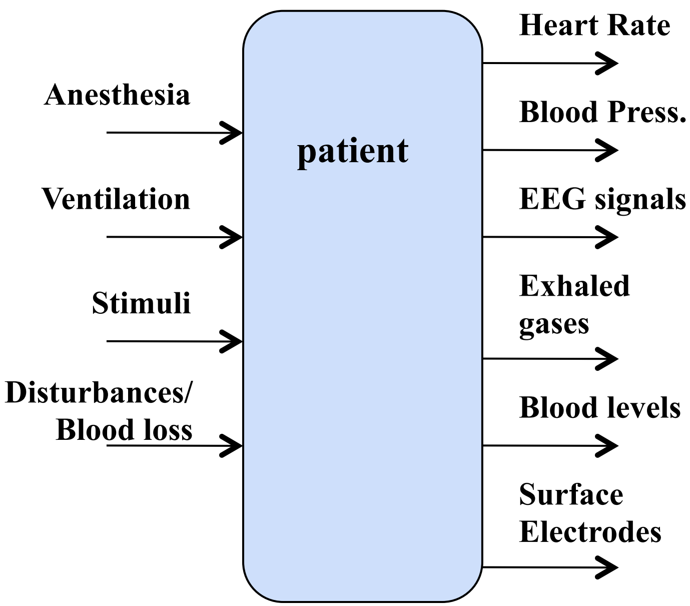

Model-based feedback control requirements:

- means of sensing levels of sedation, analgesia, relaxation/neuromuscular blockade
- mathematical models of patient response

Goal: automate/optimize delivery and control of anesthesia

Problem Statement
Anesthesia Control during Surgery

Sensing signals:

- **Neuromuscular block:** *Surface electrode or piezoelectric measurements of response to electrical stimuli; typically uncoupled from sedation effects*
- **Analgesia:** *No standardized or widely accepted means of measuring extent of pain relief; appears to be correlated with sedation*
- **Sedation:** *Spectral entropies (GE), wavelet analysis methods, Bispectral Index (BIS)*

Derived from EEG using combination of higher order spectra and other indicators such as spectral edge and median frequencies; reveals synchrony of cortical brain signals characterizing unconsciousness (Covidien)

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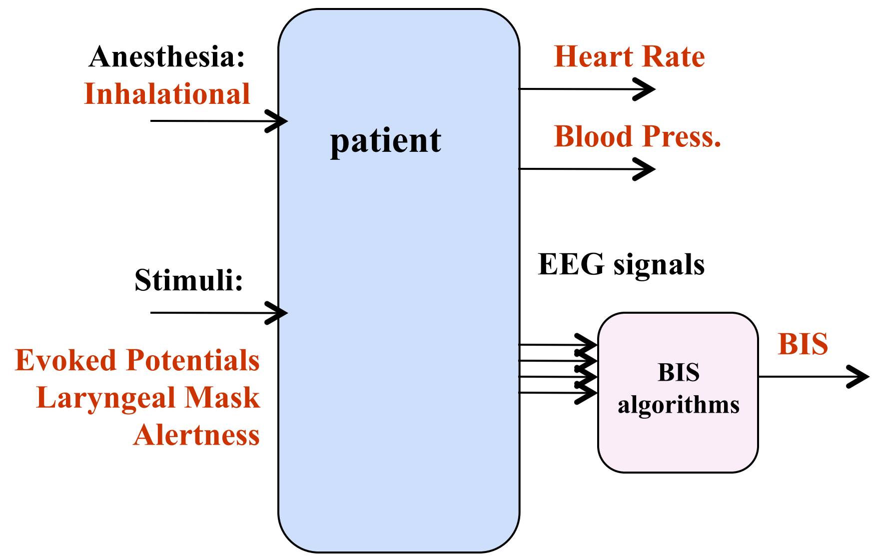
Anesthesia Control during Surgery

Model-based feedback control:

- Inputs: inhalational sedative Isoflurane and clinical stimuli
- Outputs: vital signs Heart Rate (HR) and Mean Arterial Pressure (MAP); BIS
- BIS values range from 0 to 100:
  100 – completely alert
  60 – moderately sedated
  40 – deeply sedated



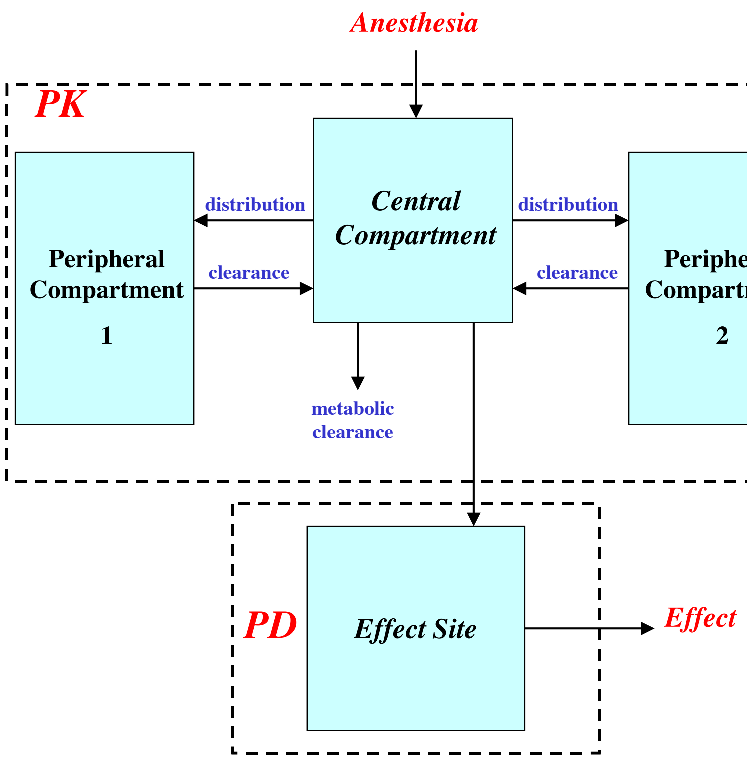
Control Goals:

- *Track BIS reference trajectory signal while maintaining HR and MAP in healthy ranges*
- *Must be adaptive and robust to patient variability*

Patient Response Models

Modeling Patient Response

Compartment Models

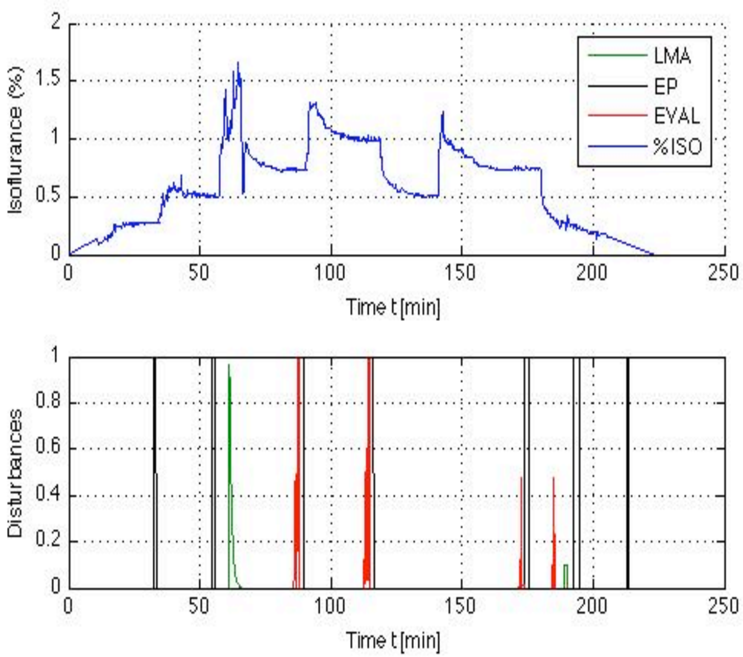


- ***Pharmacokinetic (PK) models:*** Empirically derived linear ODEs
- ***Pharmocodynamic (PD) models:*** Static nonlinearity (e.g., sigmoidal function) fit to individual patient data
- ***Nonlinear SISO Grey-Box Models***

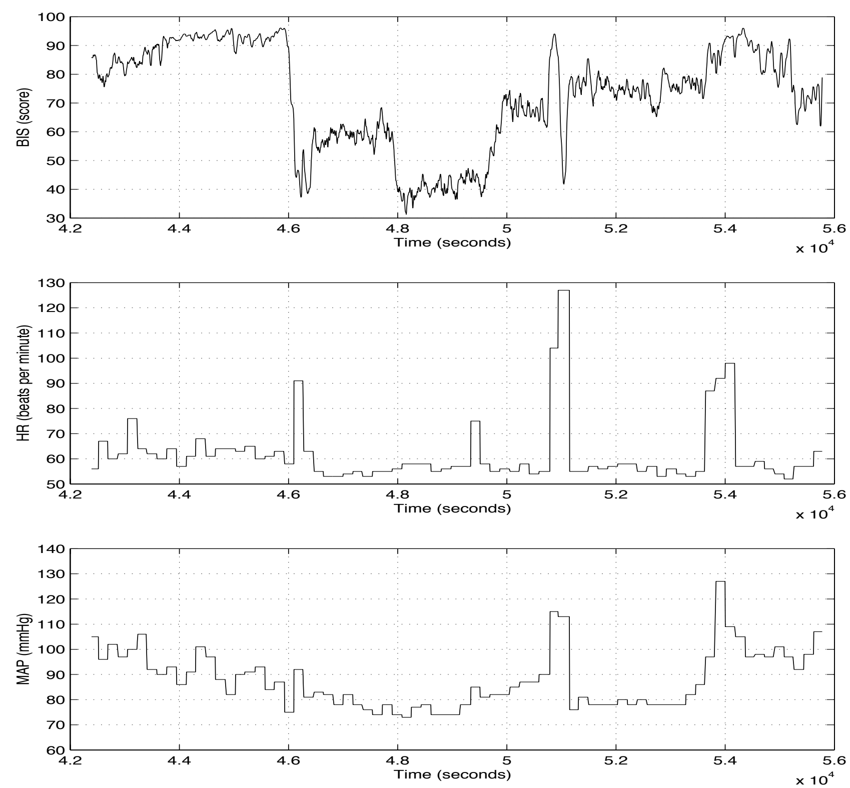
Modeling Patient Response

Clinical trial data

Input Data



Output Data



P. S. Glass, M. J. Bloom, et. al, Anesthesiology, 1997

Modeling Patient Response

Linear Parameter Varying (LPV) Models: Subspace Identification used to construct models for individual patients from clinical data

- *Piecewise-linear models*
  - Awake and Sedated patient states
  - Low-order (3rd to 5th order per patient state)

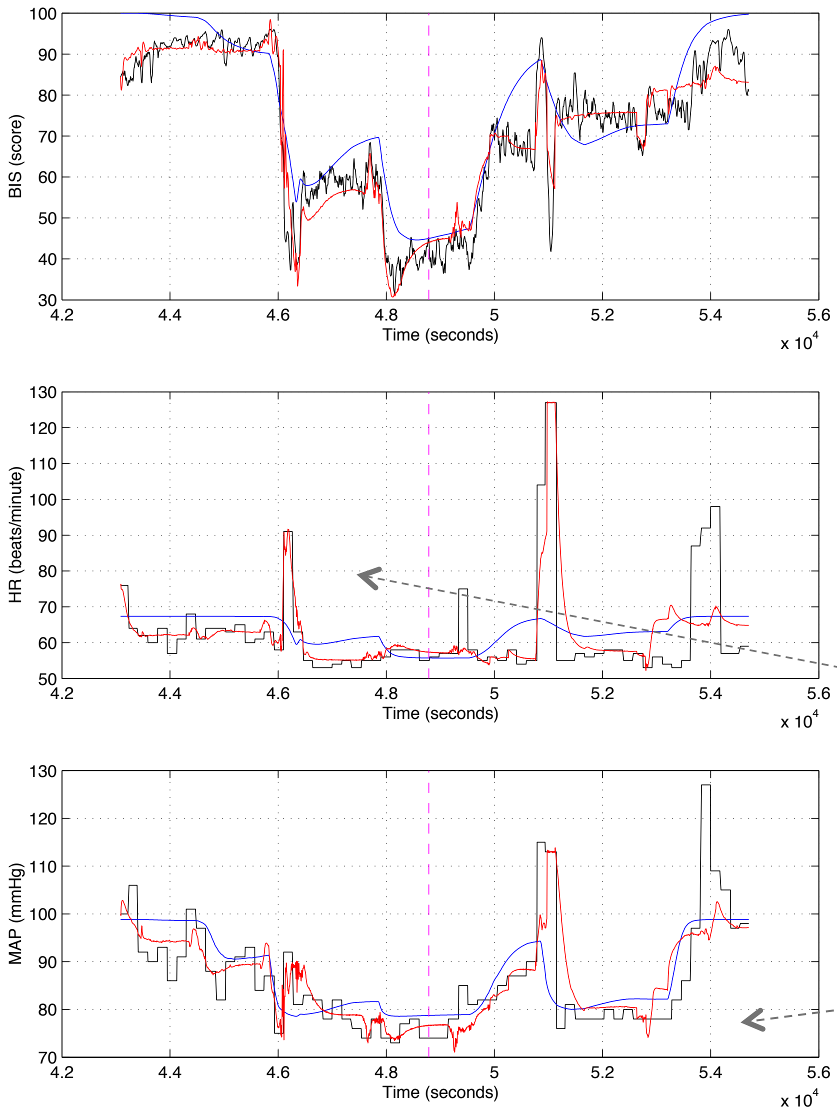
$$
\begin{aligned}
x_i(k+1) &= A_i x_i(k) + B_i u(k) + w(k) \\
y(k) &= C_i x_i(k) + D_i u(k) + v(k) \\
where\ \ i &= A\ (\text{Alert}),\ \ S\ (\text{Sedated})
\end{aligned}
$$

- *LPV models*
  - Gain-scheduled with respect to BIS value

$$
\left.
\begin{aligned}
A(\delta) &= \tfrac{\delta(\delta-1)}{2} A_A + \tfrac{\delta+1}{2} A_S \\
B(\delta) &= \tfrac{\delta(\delta-1)}{2} B_A + \tfrac{\delta+1}{2} B_S \\
C(\delta) &= \tfrac{\delta(\delta-1)}{2} A_A + \tfrac{\delta+1}{2} A_S \\
\\
with\ \ \delta(t) &= 1 - \tfrac{2}{1+\exp^{\eta*(70-BIS(t))}}
\end{aligned}
\right\}
\begin{aligned}
&G(\delta(t),\lambda) = \\
&C(\delta)\left(\lambda I - A(\delta)\right)^{-1} B(\delta)
\end{aligned}
$$

Modeling Patient Response

LPV model simulation results



Patient 1 data and models:

- *Measured data*
- *Reduced order LPV model*
- *Compartment model*

Estimation data

Validation data

H. H. Lin, C. L. Beck, and M. J. Bloom, IEEE Trans. on Biomed. Eng., 2004.

Modeling Patient Response

- $\mathcal{L}_1$-Adaptive output feedback control design method based on standard transfer function models
  - **Model structure**

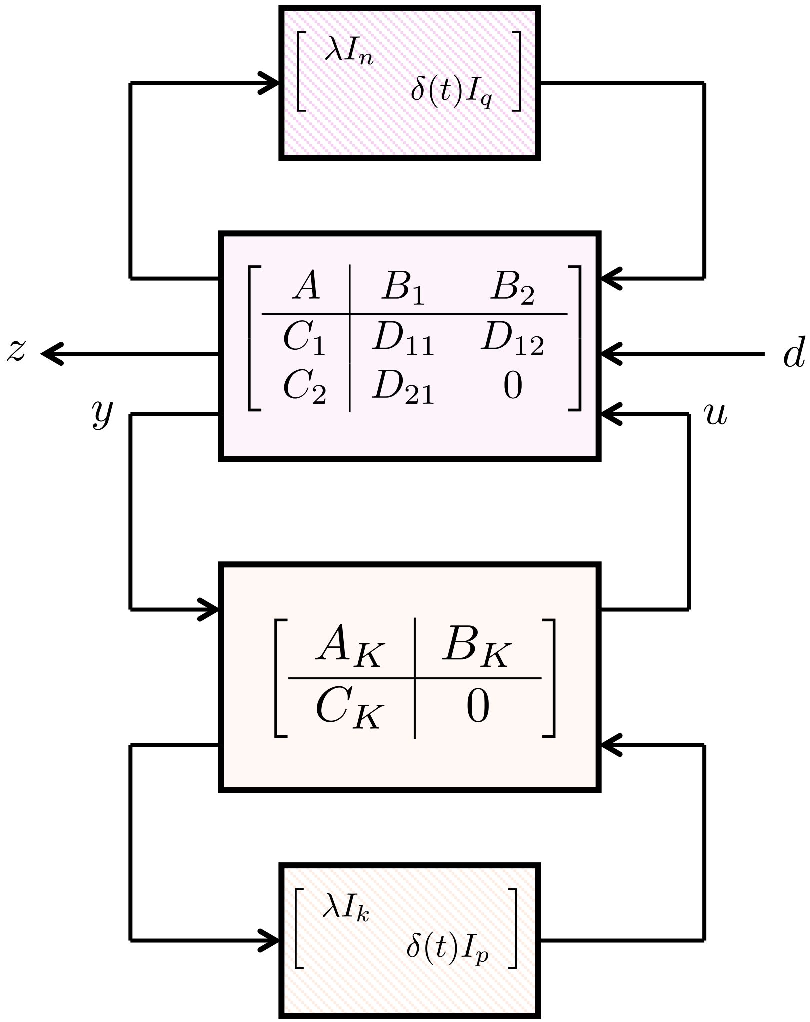
$$\boxed{y(s) = G(s)\left(u(s) + d(s)\right)}$$

  - *G(s)* is LTI system transfer function; assumed strictly proper
  - *y(t)* is measured BIS reading
  - *u(t)* is input anesthesia flow *(percentage concentration of volume)*
  - *d(t)* is time-varying disturbance *(may be a function of y(t), assumed Lipshitz with constant L)*

- State-Space Identification methods used to construct 4th order realizations *{A, B, C}*: $\boxed{G(s) = C(sI - A)^{-1}B}$

LPV and $\mathcal{L}_1$-Adaptive Control

LPV Controller Synthesis



Find R, S, X and Y:

- $N_R^T \begin{bmatrix} ARA^T - R & ARC_1^T & B_1 \\ C_1RA^T & C_1RC_1^T - Y & D_{11} \\ B_1^T & D_{11}^T & -X \end{bmatrix} N_R < 0$

- $N_S^T \begin{bmatrix} A^TSA - S & A^TSB_1 & C_1^T \\ B_1^TSA & B_1^TSB_1 - X & D_{11}^T \\ C_1 & D_{11} & -Y \end{bmatrix} N_S < 0$

- $\begin{bmatrix} R & I \\ I & S \end{bmatrix} \geq 0$ and $\begin{bmatrix} X & I \\ I & Y \end{bmatrix} \geq 0$

- $rank(I - RS) \leq k$

A. Packard, System and Control Letters, 1994; Apkarian and Gahinet, IEEE Trans. on Auto. Control, 1995; S. Shahruz and S. Behtash, J. of Math. Analysis and Applications, 1992

$\mathcal{L}_1$-Adaptive Control Methods

Overview

- Goal: track a given reference input *r(t)* under modeling uncertainties
- Guarantee: asymptotic tracking with uniformly bounded system inputs and outputs
- *Prevents high frequency oscillations in control channel, and parameter drifts*

C. Cao and N. Hovakimyan, IEEE Trans. on Auto. Control, 2008

$\mathcal{L}_1$-Adaptive Control Methods

Overview

- Design controller such that output *y(t)* tracks reference input *r(t)* according to some desired model *M(s)*: $y(s) \approx M(s)r(s)$

- Rewrite original input-output relationship using reference model:

$$\begin{aligned} y(s) &= M(s)\left(u(s)+\sigma(s)\right), \quad where \\ \sigma(s) &= \tfrac{(G(s)-M(s))u(s)+G(s)d(s)}{M(s)} \end{aligned}$$

- <u>*Example:*</u> $M(s) = \dfrac{m}{s+m}$

$\mathcal{L}_1$-Adaptive Control Methods

Design Architecture

Consider the closed-loop reference system:

$$
\begin{aligned}
y_{ref}(s) &= M(s)\left(u_{ref}(s) + \sigma_{ref}(s)\right) \\
\sigma_{ref} &= \tfrac{(G(s)-M(s))u_{ref}+G(s)d(s)}{M(s)} \\
u_{ref} &= C(s)(r(s) - \sigma_{ref}(s)), \quad with \\
C(s) &= \tfrac{w}{s+w}
\end{aligned}
$$

- *C(s)* is low-pass filter used to attenuate high frequency uncertainty in control channel, and w is a design parameter
- *r(s)* is reference input

$\mathcal{L}_1$-Adaptive Control Methods

Design Architecture

Enforce the following stability condition:

Select *C(s)* and *M(s)* such that

$$H(s) = \frac{G(s)M(s)}{(C(s)G(s) + (1 - C(s))\,M(s)}$$

is BIBO stable, and

$$L \cdot \|H(s)(1 - C(s))\|_{\mathcal{L}_1} < 1$$

Guarantees BIBO stability of closed-loop reference system

$\mathcal{L}_1$-Adaptive Control Methods

Design Architecture

The $\mathcal{L}_1$-Adaptive Controller consists of

- ***Output Predictor:***

$$\frac{d\tilde{y}(t)}{dt} = -m\tilde{y}(t) + m\left(u(t) + \tilde{\sigma}(t)\right), \quad \tilde{y}(0) = 0$$

- ***Parameter Adaptation Law:***

$$\frac{d\tilde{\sigma}(t)}{dt} = \Gamma \cdot \Pi(\tilde{\sigma}(t),\ -mP(\tilde{y} - y)), \quad \tilde{\sigma}(0) = 0$$

where $\Pi(\cdot,\cdot)$ is least-squares type projection operator, Γ is adaptation rate, $P > 0$ is arbitrary, and $|\tilde{\sigma}(t)| \leq \Delta$ is projection bound

- ***Feedback Control Law:*** $u(s) = C(s)(r(s) - \tilde{\sigma}(s))$

$\mathcal{L}_1$-Adaptive Control Methods

Performance Guarantees

It can be shown that for all $t \geq 0$, *the* $\mathcal{L}_1$*-Adaptive Output Feedback Controller guarantees uniform boundedness of the tracking error, i.e.,*

$$\boxed{\|\tilde{y}(t) - y(t)\|_{\mathcal{L}_\infty} \leq \frac{k}{\sqrt{\Gamma P}}}$$

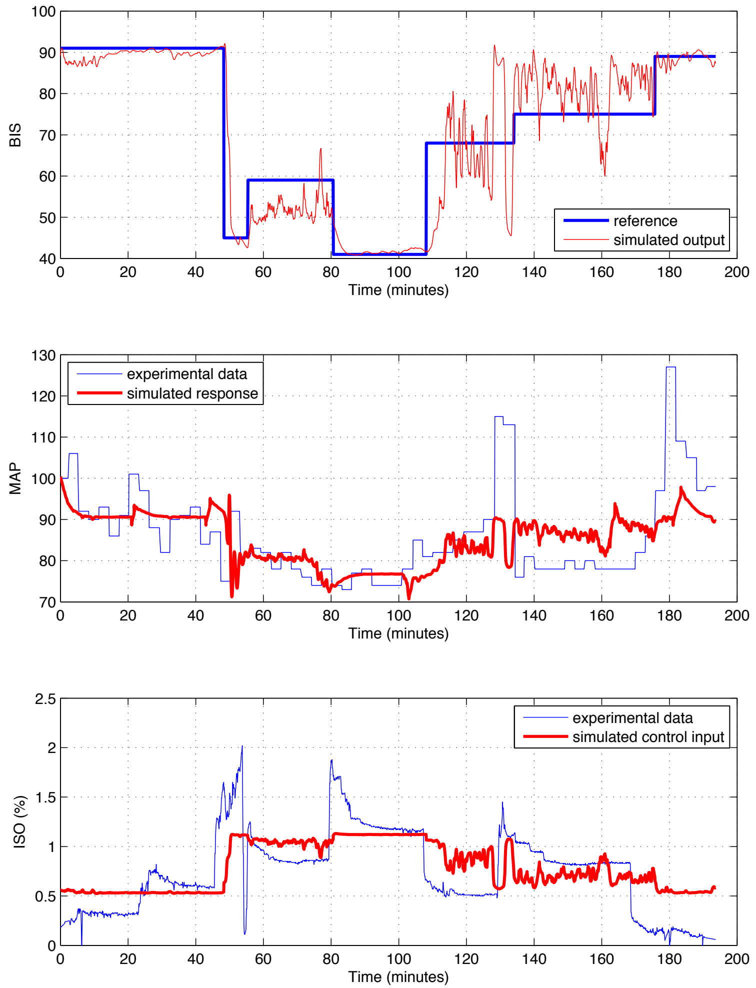
where k is a (computable) constant

Design and Simulation Results

LPV Design and Simulation Results

BIS reference tracking

Patient 1 LPV controller, patient 1 model:

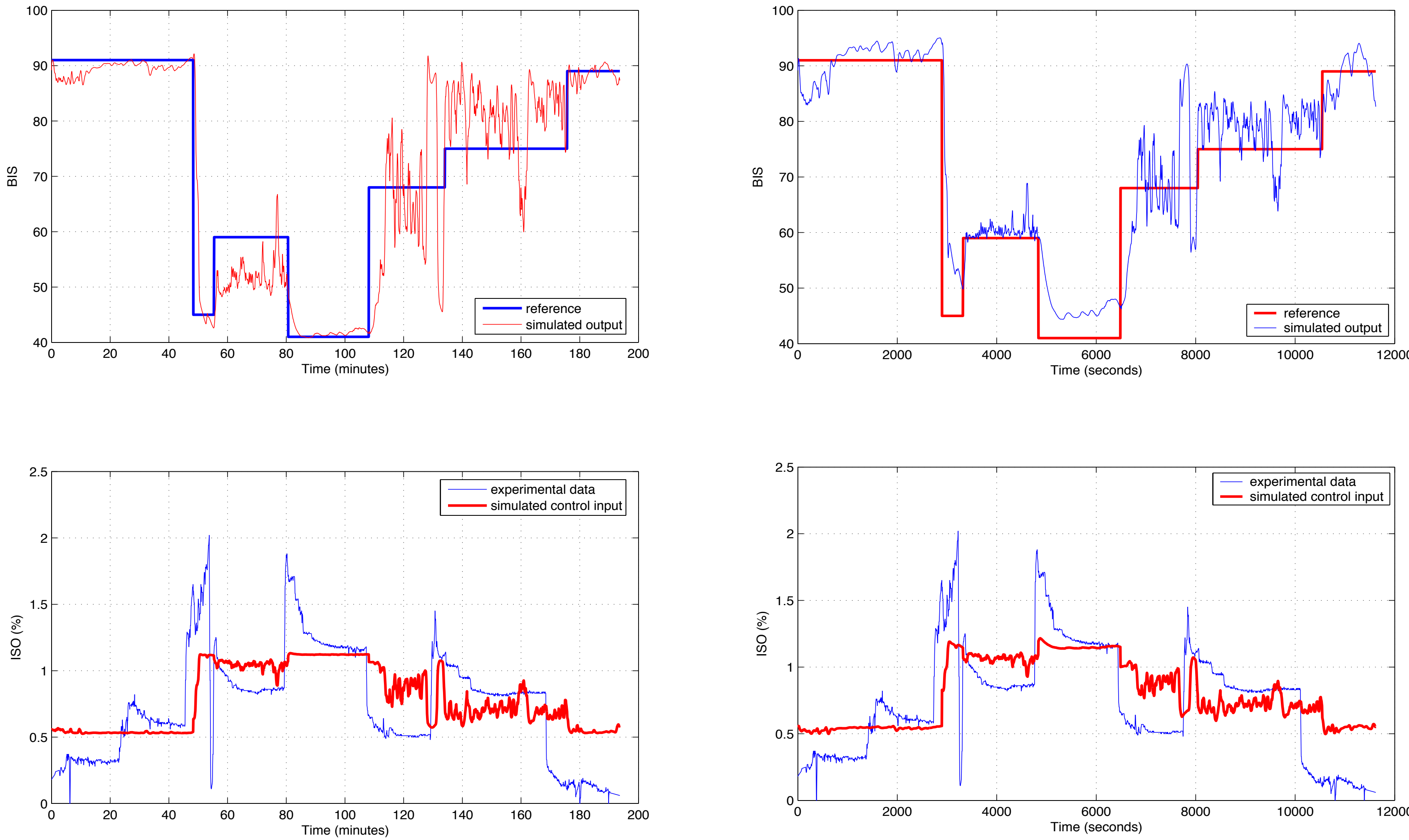


- Reference signal *r(t)* constructed to emulate original BIS profiles in clinical data
- BIS signal should track *r(t)*
- MAP within 60-110mmHg

LPV Design and Simulation Results

BIS reference tracking

Patient 1 model: Patient 1 LPV controller and Patient 3 LPV controller

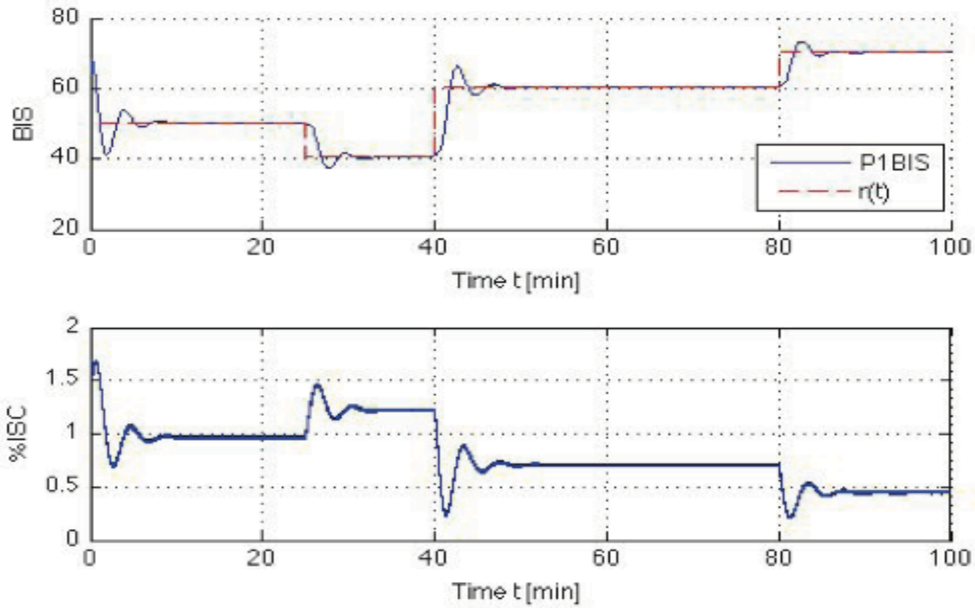


H. H. Lin, C. L. Beck and M. J. Bloom, ACC, 2008

$\mathcal{L}_1$-Adaptive Design and Simulation Results

BIS Tracking – No Disturbances

Patient 1 adaptive output feedback control:

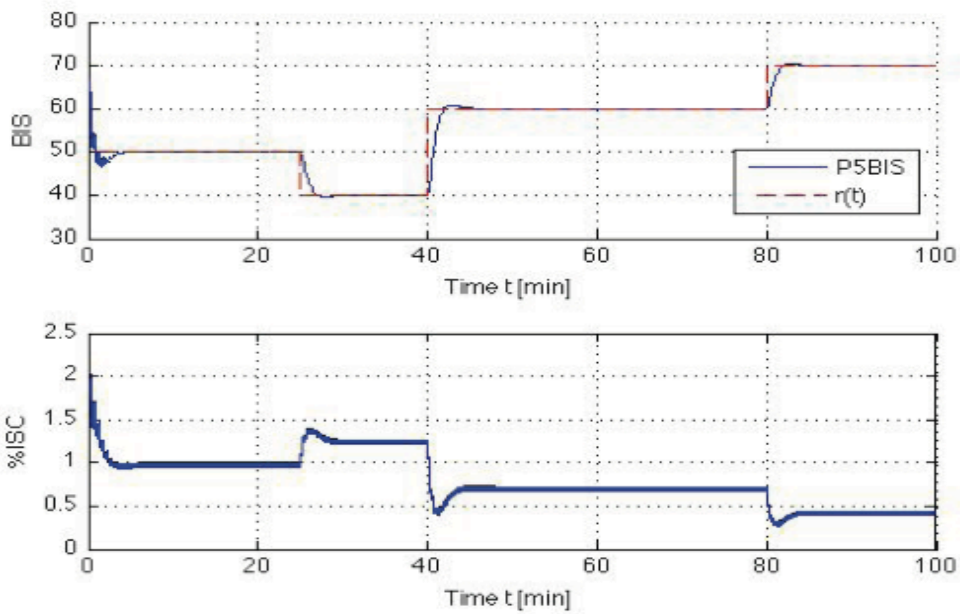


- ***design parameters***
  - *initial settings:* $P = 1, \quad \Delta = 100, \quad \Gamma = 50,000$
  - *filters:* $M(s) = \frac{1}{30s+1}, \quad C(s) = \frac{0.001}{s+0.001}$

$\mathcal{L}_1$-Adaptive Design and Simulation Results

BIS Tracking – No Disturbances

Patient 5 adaptive output feedback control:

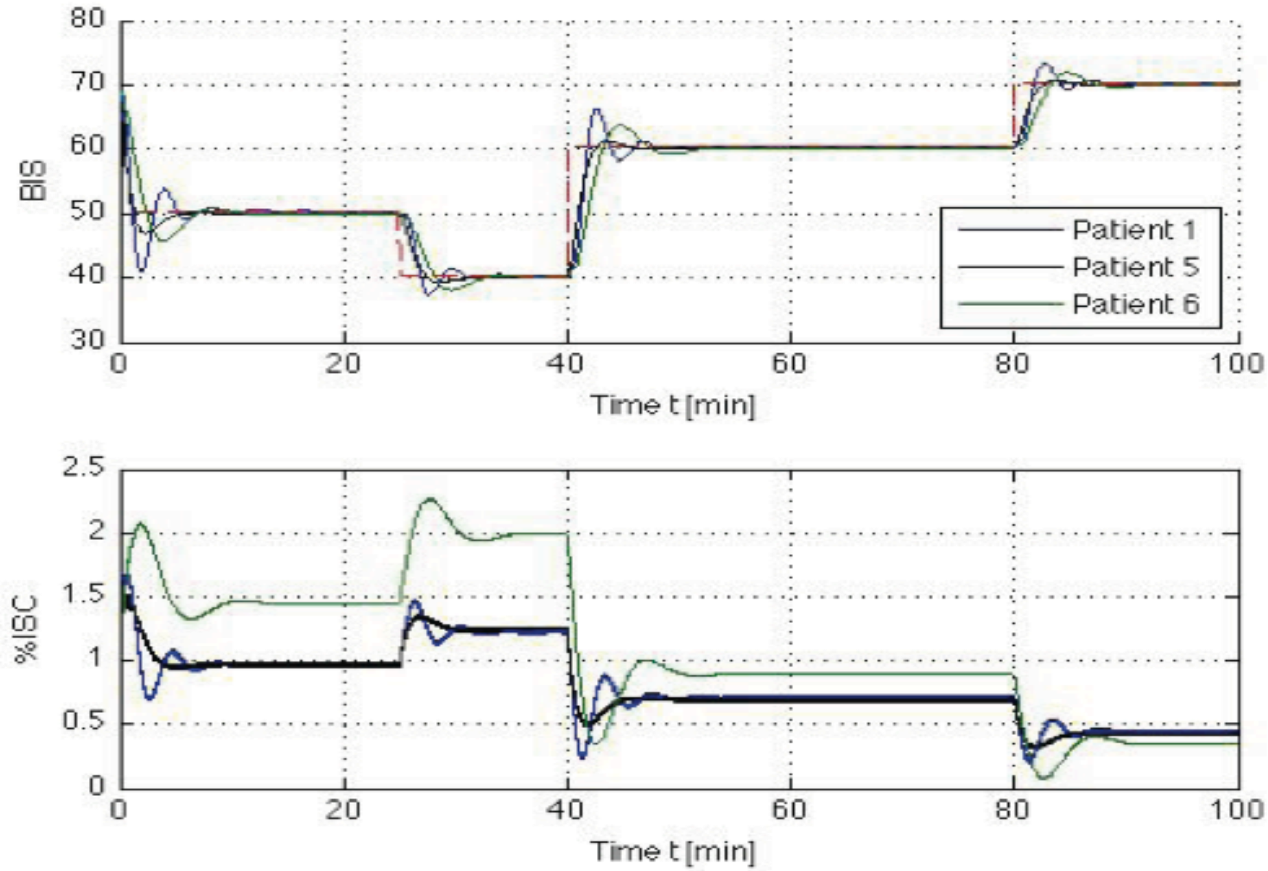


- ***design parameters***
  - *initial settings:* $P = 1, \quad \Delta = 100, \quad \Gamma = 50,000$
  - *filters:* $M(s) = \frac{1}{30s+1}, \quad C(s) = \frac{0.002}{s+0.002}$

$\mathcal{L}_1$-Adaptive Design and Simulation Results

BIS Tracking – Robustness to Patient Variability

Patient 1 controller used on Patient 2, 3, 5, 6 and 7 models



$\mathcal{L}_1$-Adaptive Design and Simulation Results
BIS Tracking – Robustness to Patient Variability

Patient 1 controller on Patient 2, 3, 5, 6 and 7 models: *Performance Analysis*

Patient	1	2	3	5	6	7
Residual Tracking Error	0.0019	0.0062	0.0022	0.0016	0.0036	0.0064

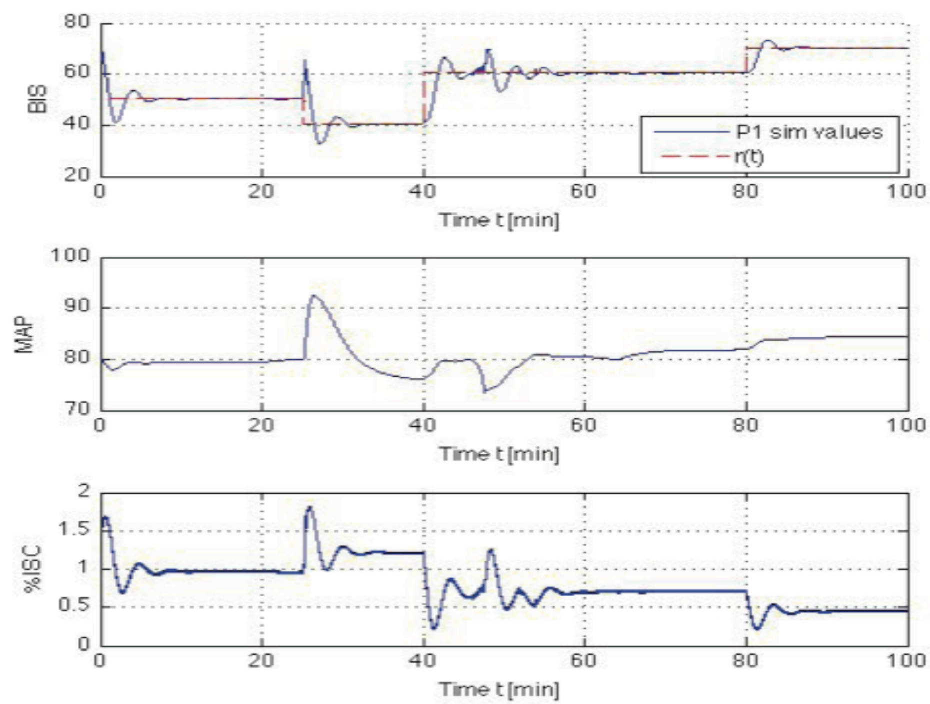
Patient	1	2	3	5	6	7
Isoflurane Use (liters)	2.40	2.86	2.23	2.40	2.29	2.15

Previous control yielded residual tracking errors in the 5-10% range, and average total isoflurane consumption of approximately 3 liters

$\mathcal{L}_1$-Adaptive Design and Simulation Results

MIMO Control – BIS Tracking and MAP Performance with Disturbances

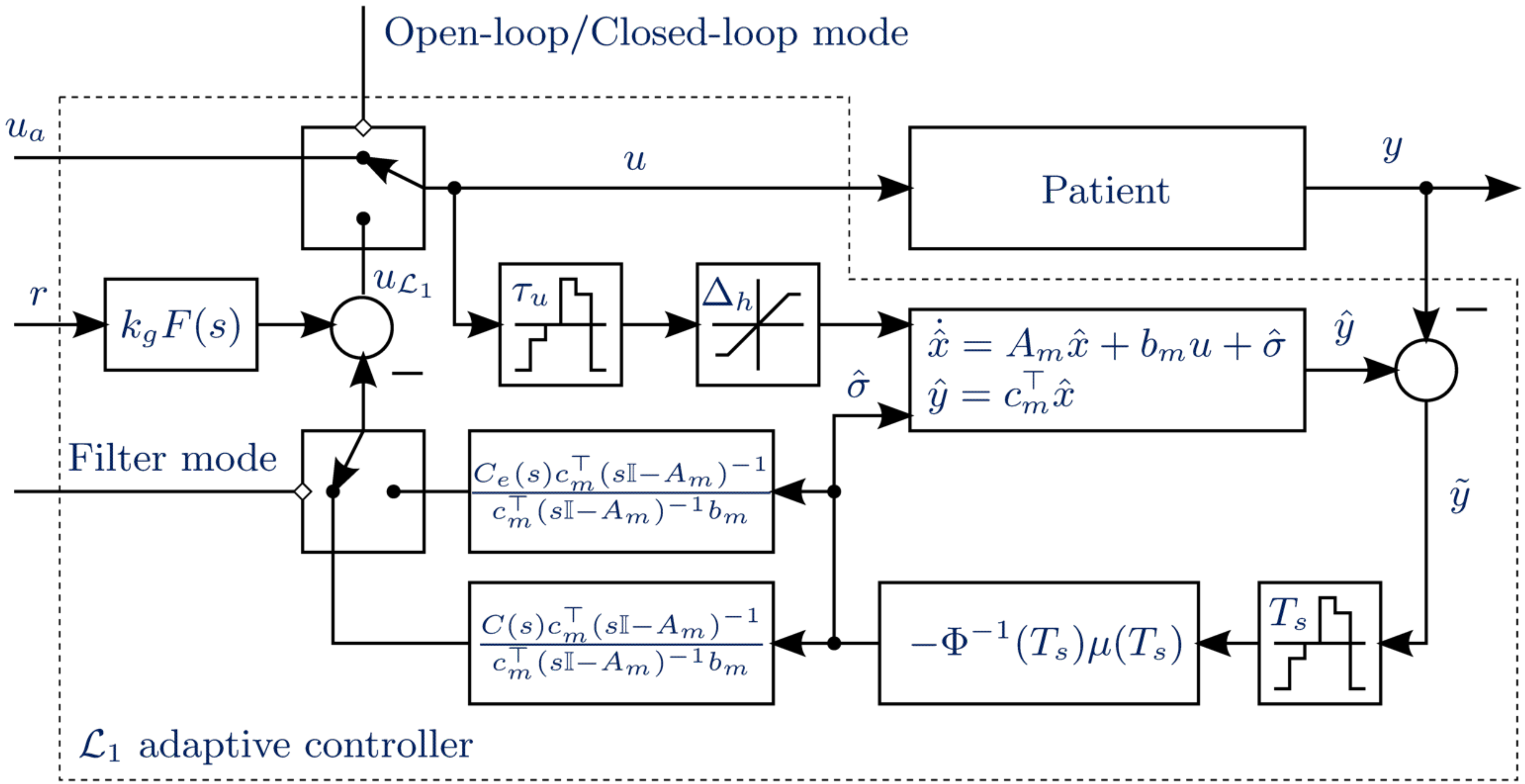
Patient 1 Multivariable controller – 2 inputs, 2 outputs:



MAP required to be maintained within 60-110 mmHg range

M. Ralph, C. L. Beck and M. J. Bloom, ACC 2011; E. Kharisov, C. L. Beck and M. J. Bloom, SIAM Conference, 2013

$\mathcal{L}_1$ - Adaptive Controller Designs



Conclusions

- First applications of LPV and $\mathcal{L}_1$-Adaptive methods to anesthesia control
- Performance analysis includes intended patient and cross-patient evaluations
- **Implementation issues:**
  - *Anesthesiologist controlled induction*
  - *Enforce bounds on maximum drug concentrations – "Hedging design"*
  - *Predictor sampling*
  - *$\mathcal{L}_1$/ LPV controllers with enable-disable control: "Human-Machine Interface"*
  - *Multiple synergistic anesthetic agents*

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