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Control strategies for optimized drug administration in general anesthesia

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February 11, 2019

Acknowledgments

Luca Merigo, University of Brescia
Fabrizio Padula, Curtin University
Nicola Latronico, University of Brescia and Spedali Civili di Brescia
Massimiliano Paltenghi, Spedali Civili di Brescia
Clara Ionescu, University of Gent
Teresa Mendonca, University of Porto
Andrzej Pawlowski and José Luis Guzman, University of Almeria
Sebastian Dormido, UNED

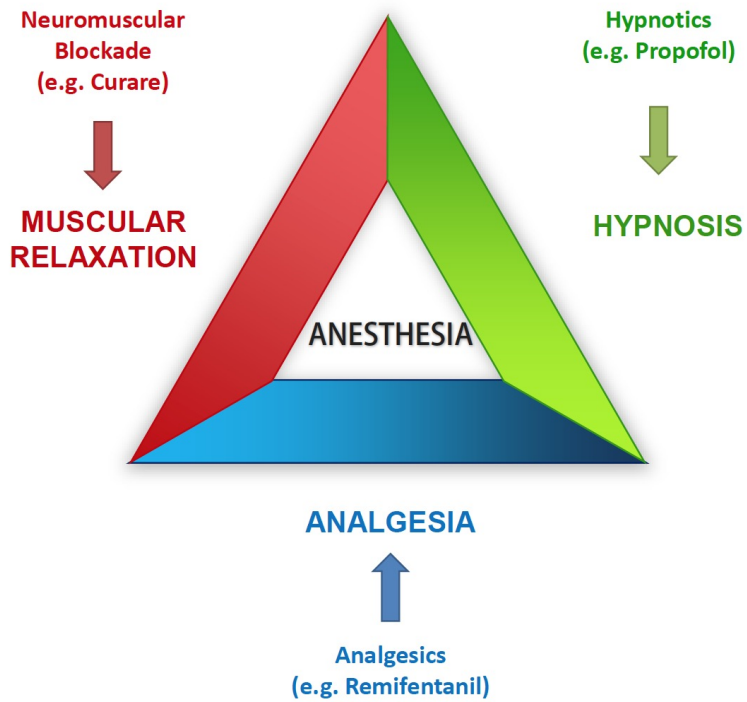
Outline

What is anesthesia?

“you sleep while the surgeon cuts, and you do not feel”

Better...what is anesthesia?

Anesthesia: pharmacologically induced, temporary and reversible state, resulting in inhibition of sensitivity, consciousness and pain, associated with muscle relaxation.



3 MAIN COMPONENTS

- Muscle relaxation $\longrightarrow$ **Neuromuscular blockade**
- Pain $\longrightarrow$ **Analgesia**
- Consciousness $\longrightarrow$ **Hypnosis**

Neuromuscular blockade

The patients should NOT move during surgery, specific drug such as curare are used to induce neuromuscular blockade.

- extensively studied in the literature
- well-defined and **clinically accepted** measurement techniques $\rightarrow$ we have feedback
- **no interaction with other components** of anesthesia$\rightarrow$ a SISO control problem

Hypnosis & Analgesia

Hypnosis is the loss of consciousness, it is induced through intravenous injection of the hypnotic drug **propofol**

Analgesia is the absence of pain, it is induced through intravenous injection of the analgesic drugs **remifentanil**

Hypnosis is not enough. At unconscious level the central nervous system feels pain: increased heart rate, sweating, traumatizing post-operatory recovery, etc.

Why together?!

- propofol and remifentanil exhibit **strong interaction**
- **no reliable measure of pain**

This has to be avoided...

How does the anesthesiologist work?

He/she decides the **infusion rates** of hypnotic and anesthetic depending on

- experience (feeling of “what is going on”)
- knowledge of the surgical procedure
- non-measurable physiological signs: facial grimacing, lacrimation, diaphoresis, frequent urination, etc.
- measurable physiological signs: blood pressure, heart rate, saturation, etc.
- quantitative feedback from EEG (electroencephalogram)
- model-based standard procedures

Quantitative feedback of depth of hypnosis (DoH)

- EEG related indexes are the only **clinically accepted measures**
- both propofol (hypnotic) and remifentanil (analgesic) affect the EEG: **drugs interaction**

EEG elaborations is referred to as DoH, but it gives a combined measure of hypnosis and analgesia

The most common measure of DoH is an elaboration of the EEG called **BISPECTRAL INDEX SCALE**

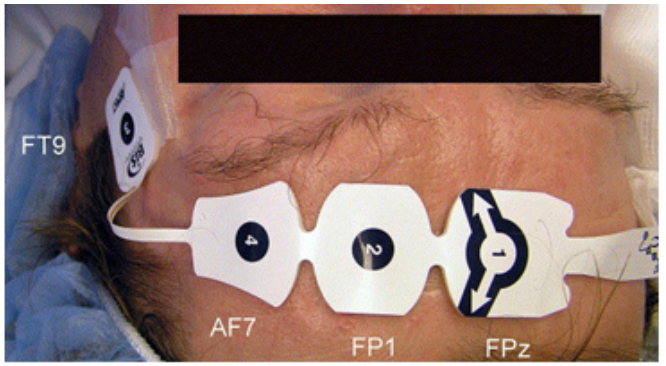
Bispectral Index Scale (BIS)

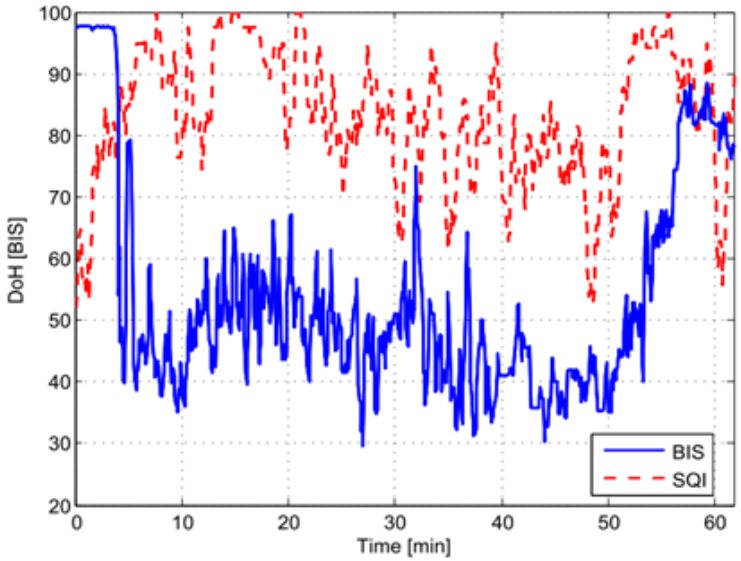
The BIS is an aggregate of EEG signal (Aspect Medical Systems Inc, Norwood, Massachusetts).

BIS	EEG
0	flat
40	deep hypnosis
60	moderate hypnosis
80	reaction to aural stimuli
100	fully awake patient

The target BIS during surgery is 50.

Any value in the range [40 60] is acceptable.

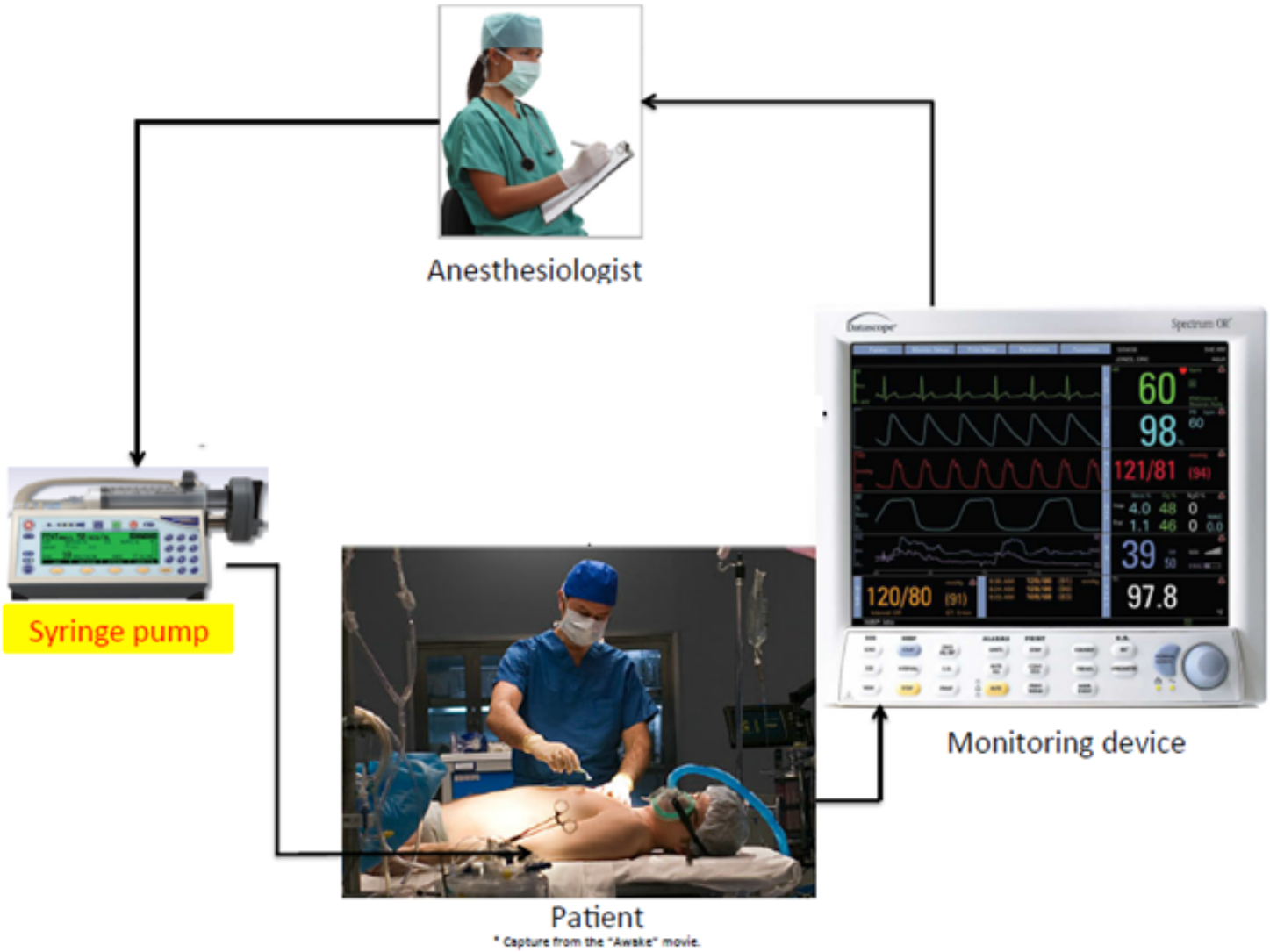




Strong noise

Additive white Gaussian noise with power spectral density $PSD = 39.3392$

Summarizing, we are here



Problems...

Approximately 4.5 million major surgical procedures are undertaken in Italy each year.

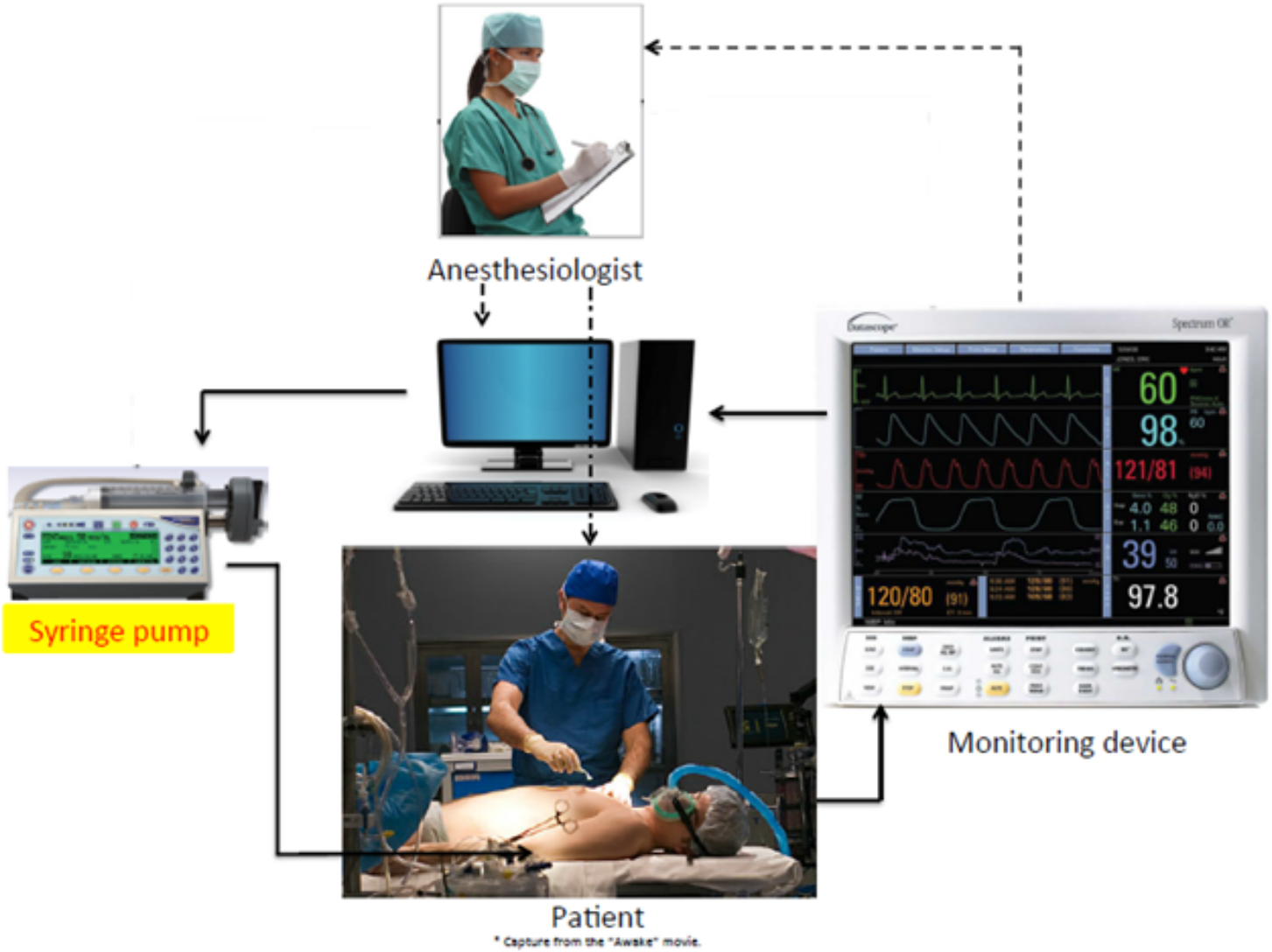
Postoperative nausea and vomiting (PONV) are common and distressing to patients (about 30%).

Prolonged post-anesthesia care unit stay significant increase in overall **health care costs**.

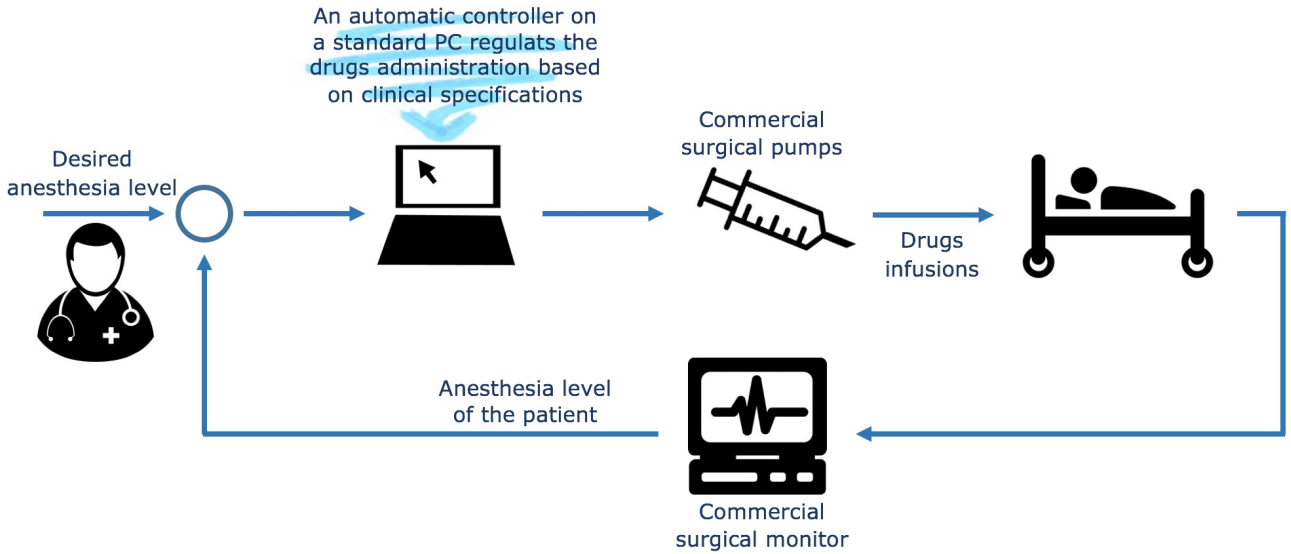
Anesthesia awareness (AA) is postoperative recall of events experienced under general anesthesia. Post-traumatic stress disorder appears in 33%-56% of patients who experienced AA during general anesthesia: depression, anxiety, sleep disturbances, nightmares, panic attacks may appear even after 2 years and more.

To avoid (AA) the anesthesiologist tends to overdose $\rightarrow$ **health care costs** and **patient safety**.

Solution!


Anesthesiologist
Syringe pump
Monitoring device
Patient
* Capture from the "Awake" movie.

Objectives



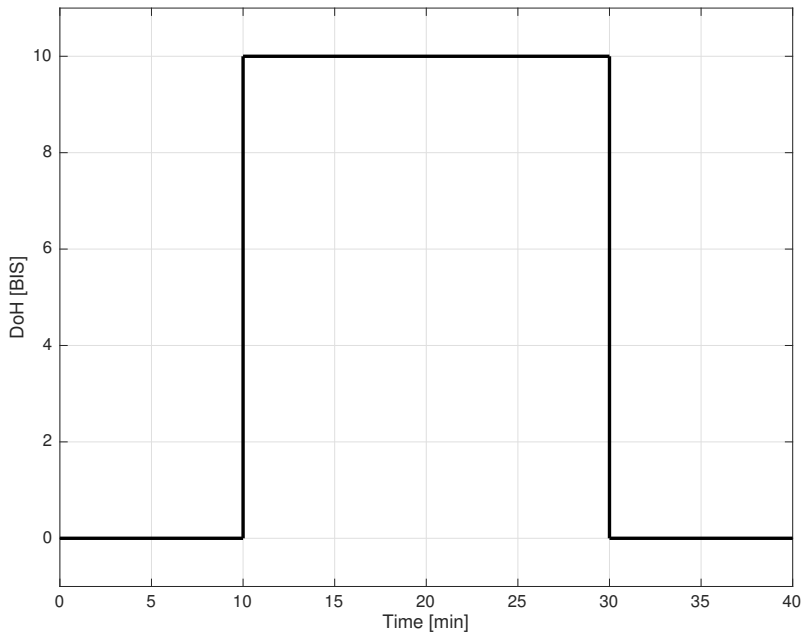
Pros:

- decrease anesthetist workload
- avoid problems caused by distraction or fatigue
- better anesthetic level
- less drugs administration
- better post-operative recovery
- reduction of side effects

Two phases

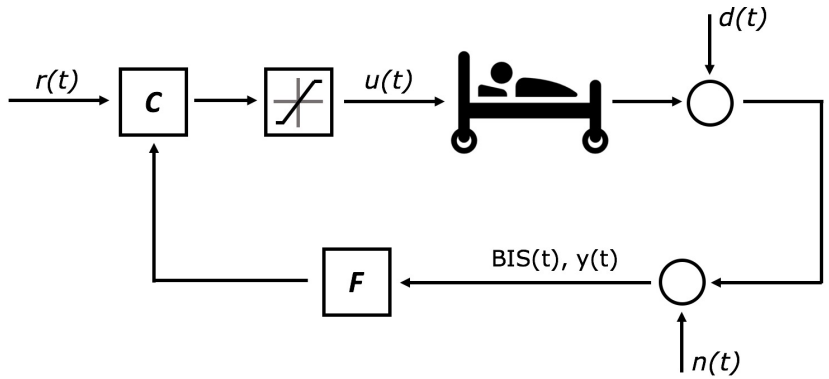
There are two main phases in anesthesia:

1. **induction phase**: the DoH is brought to the desired level $BIS = 50$
   $\rightarrow$ tracking problem
2. **maintenance phase** the DoH is maintained to $BIS = 50$ despite *unmeasurable* external stimuli (e.g., the surgeon cuts)
   $\rightarrow$ disturbance rejection problem



Noxious stimuli

The disturbance is modeled as an additive double step



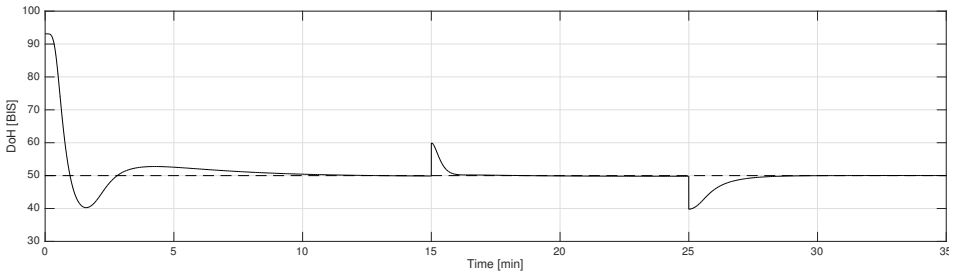
Control requirements

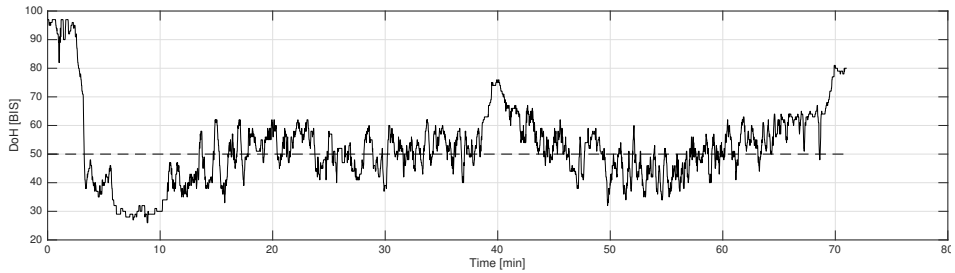
Control variable: drug infusion rate

- limited by the actuator (pump), cannot be negative
- avoid unnecessary variations of the control action

Controlled variable: DoH(BIS)

- Fast set-point (BIS=50) tracking (4-5 [min])
- Bounded undershoots of BIS during induction phase (BIS>40)
- Fast disturbance rejection (nociceptive stimulation)
- BIS between 40 and 60 during maintenance phase
- Robustness to intra-patient variability
- Robustness to inter-patient variability

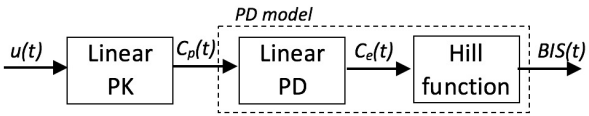




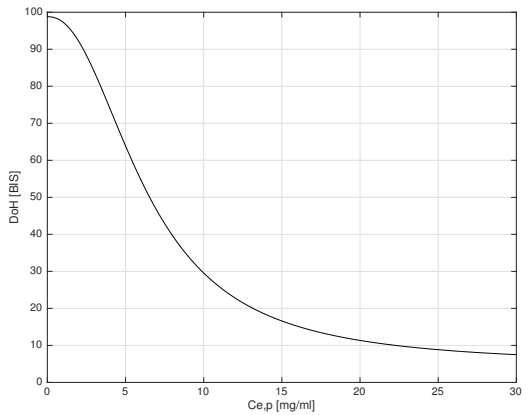
Design of the complete control structure → Tuning with optimization method **(GA/PSO)** → Control robustness validated with **Monte Carlo method**

Mathematical Models

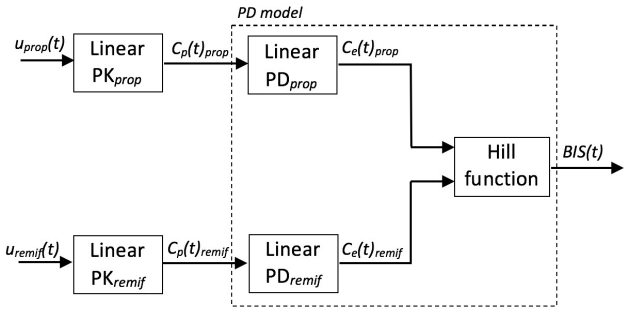
PROPOFOL MODEL:



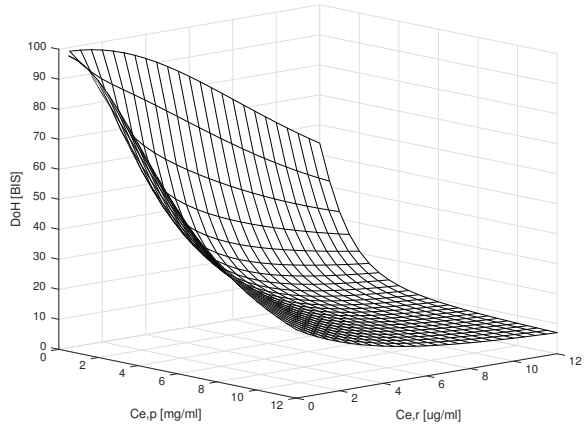
$$BIS(t) = E_0 - E_{max}\left(\frac{C_e(t)^{\gamma}}{C_e(t)^{\gamma} + C_{e50}^{\gamma}}\right)$$



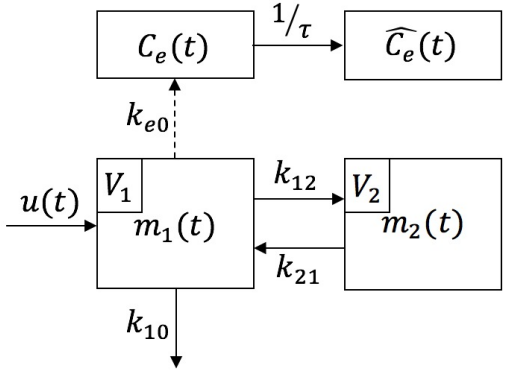
PROP+REMIF MODEL:



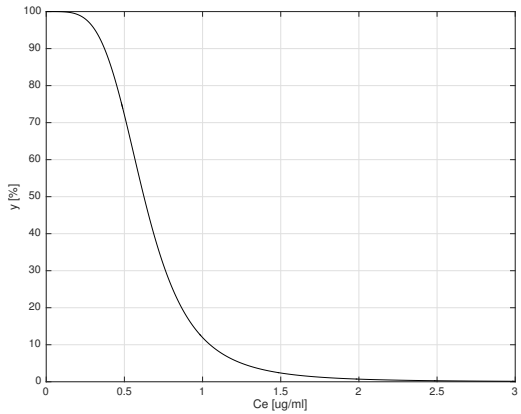
$$BIS(t) = E_0 - E_{max}\left(\frac{\left(\frac{U_{prop}(t) + U_{remif}(t)}{U_{50}(\phi)}\right)^{\gamma}}{1 + \left(\frac{U_{prop}(t) + U_{remif}(t)}{U_{50}(\phi)}\right)^{\gamma}}\right)$$



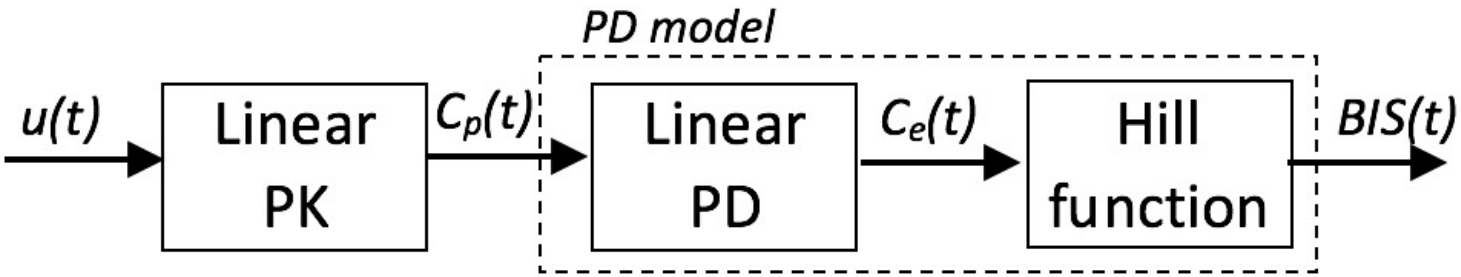
ATRACURIUM MODEL:



$$y(t) = \frac{100 \cdot C_{50}^{\gamma}}{C_{50}^{\gamma} + \hat{C}_e^{\gamma}(t)}$$



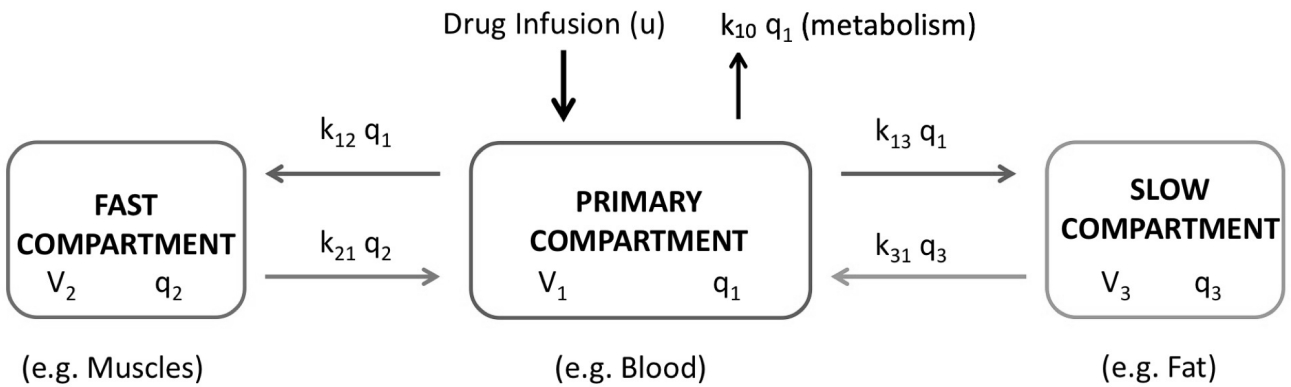
Propofol model



Pharmacokinetic (PK): dynamic of drug concentration in the human body

Pharmacodynamic (PD): relationship between drug concentration and clinical effect (BIS)

PK: mamillary three-compartment model



PK differential equation

$$\begin{aligned}\dot{q}_1(t) &= -(k_{10}+k_{12}+k_{13})q_1(t) + k_{21}q_2(t) + k_{31}q_3(t) + u(t)\\ \dot{q}_2(t) &= k_{12}q_1(t) - k_{21}q_2(t)\\ \dot{q}_3(t) &= k_{13}q_1(t) - k_{31}q_3(t)\end{aligned}$$

PD: Effect site concentration plus Hill function

Effect site: fictitious compartment to describe the lag between blood concentration and clinical effect

$$\dot{C}_e(t) = k_{1e}C_p(t) - k_{e0}C_e(t)$$

Hill function: describe response of the patient to fixed blood concentration

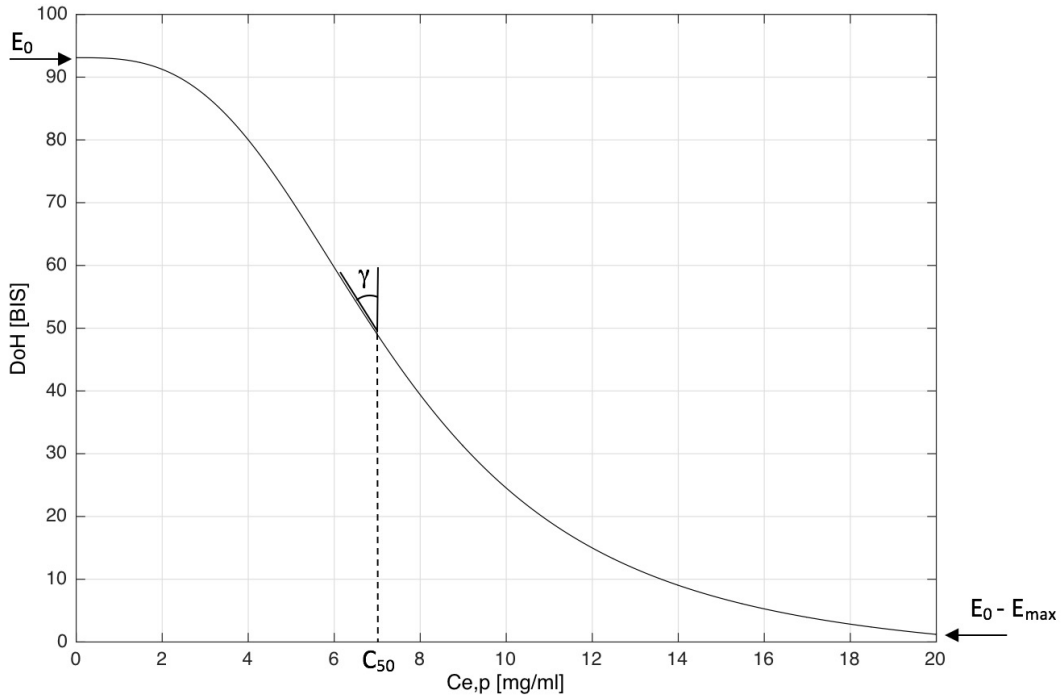
$$BIS(t) = E_0 - E_{max}\left(\frac{C_e(t)^\gamma}{C_e(t)^\gamma + C_{e_{50}}^\gamma}\right)$$

The parameter fo the linear part of the model **and their distributions** depends on the demographics of the patient[1].

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

Hill function

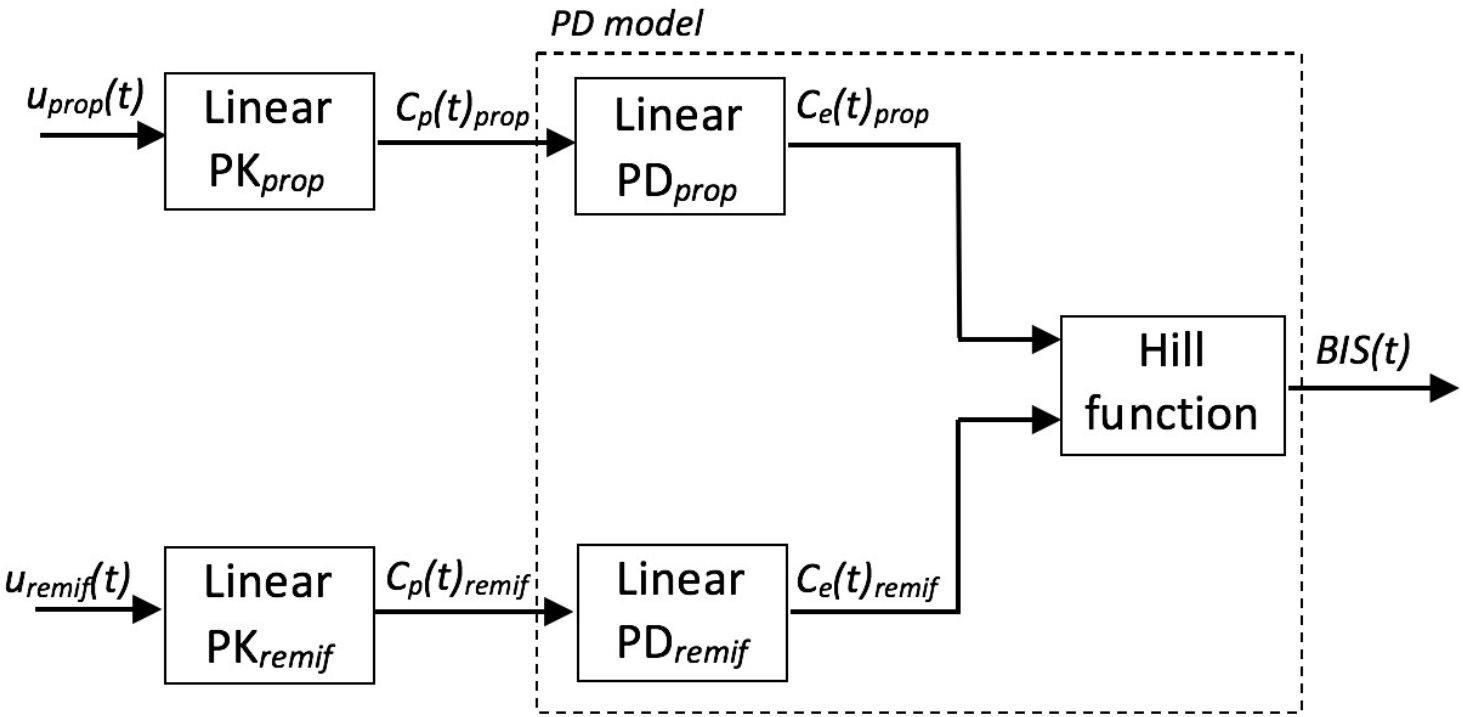
$$BIS(t) = E_0 - E_{max}\left(\frac{C_e(t)^\gamma}{C_e(t)^\gamma + C_{e50}^\gamma}\right)$$



Only the **average parameters** of the Hill function, and **their distributions** are known [2].

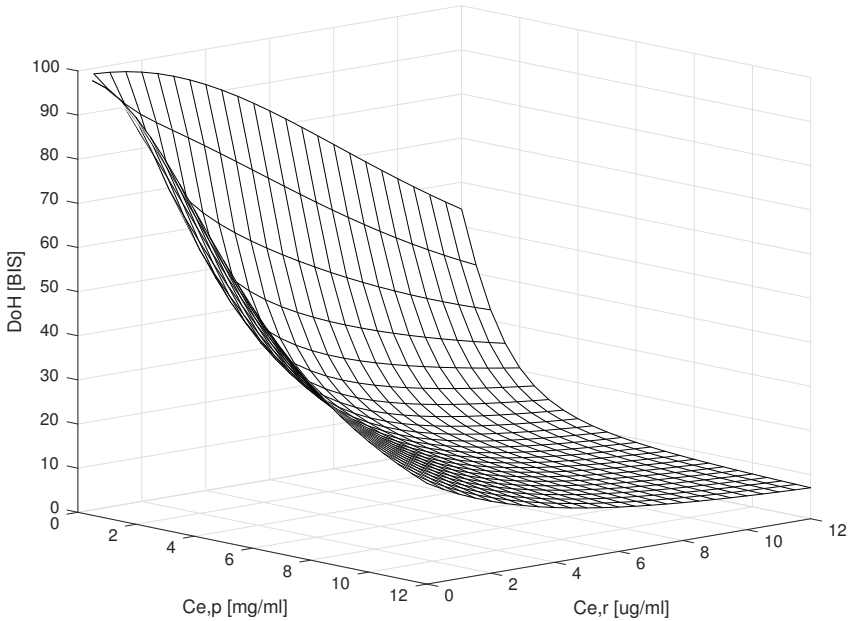
[2] A. L. G. Vanluchene, H. Vereecke, O. Thas, E. P. Mortier, S. L. Shafer, and M. M. R. F. Struys. Spectral entropy as an electroencephalographic measure of anesthetic drug effect. a comparison with bispectral index and processed midlatency auditory evoked response. *Anesthesiology*, 101:34-42, 2004.

Propofol and Remifentanil model



Remifentanil PK and linear part of the PD: same structure of the propofol model (different parameters!)

Propofol and Remifentanil model: interaction



Different combination of Propofol and Remifentanil, same BIS: a **MISO control problem**.

$$BIS(t) = E_0 - E_{max}\left(\frac{\left(\frac{U_{prop}(t)+U_{remif}(t)}{U_{50}(\phi)}\right)^{\gamma}}{1+\left(\frac{U_{prop}(t)+U_{remif}(t)}{U_{50}(\phi)}\right)^{\gamma}}\right)$$

$$U_{prop}(t) = \frac{C_{e,p}(t)}{C_{e_{50},p}},\quad U_{remif}(t) = \frac{C_{e,r}(t)}{C_{e_{50},r}},\qquad \phi = \frac{U_{prop}(t)}{U_{prop}(t)+U_{remif}(t)},\quad U_{50}(\phi) = 1-\beta\phi+\beta\phi^2,$$

Benchmark

Id	Age	H [cm]	W [kg]	G	$C_{e_{50},p}$	$C_{e_{50},r}$	γ	β	E_0	E_{max}
1	40	163	54	F	6.33	12.5	2.24	2.00	98.8	94.10
2	36	163	50	F	6.76	12.7	4.29	1.50	98.6	86.00
3	28	164	52	F	8.44	7.1	4.10	1.00	91.2	80.70
4	50	163	83	F	6.44	11.1	2.18	1.30	95.9	102.00
5	28	164	60	M	4.93	12.5	2.46	1.20	94.7	85.30
6	43	163	59	F	12.00	12.7	2.42	1.30	90.2	147.00
7	37	187	75	M	8.02	10.5	2.10	0.80	92.0	104.00
8	38	174	80	F	6.56	9.9	4.12	1.00	95.5	76.40
9	41	170	70	F	6.15	11.6	6.89	1.70	89.2	63.80
10	37	167	58	F	13.70	16.7	3.65	1.90	83.1	151.00
12	42	179	78	M	4.82	14.0	1.85	1.20	91.8	77.90
12	34	172	58	F	4.95	8.8	1.84	0.90	96.2	90.80
13	38	169	65	F	7.42	10.5	3.00	1.00	93.1	96.58

Demographics of the set of patients for propofol and remifentanil coadministration (H: height, W: weight, G: gender)

PID control scheme for Propofol and Remifentanil

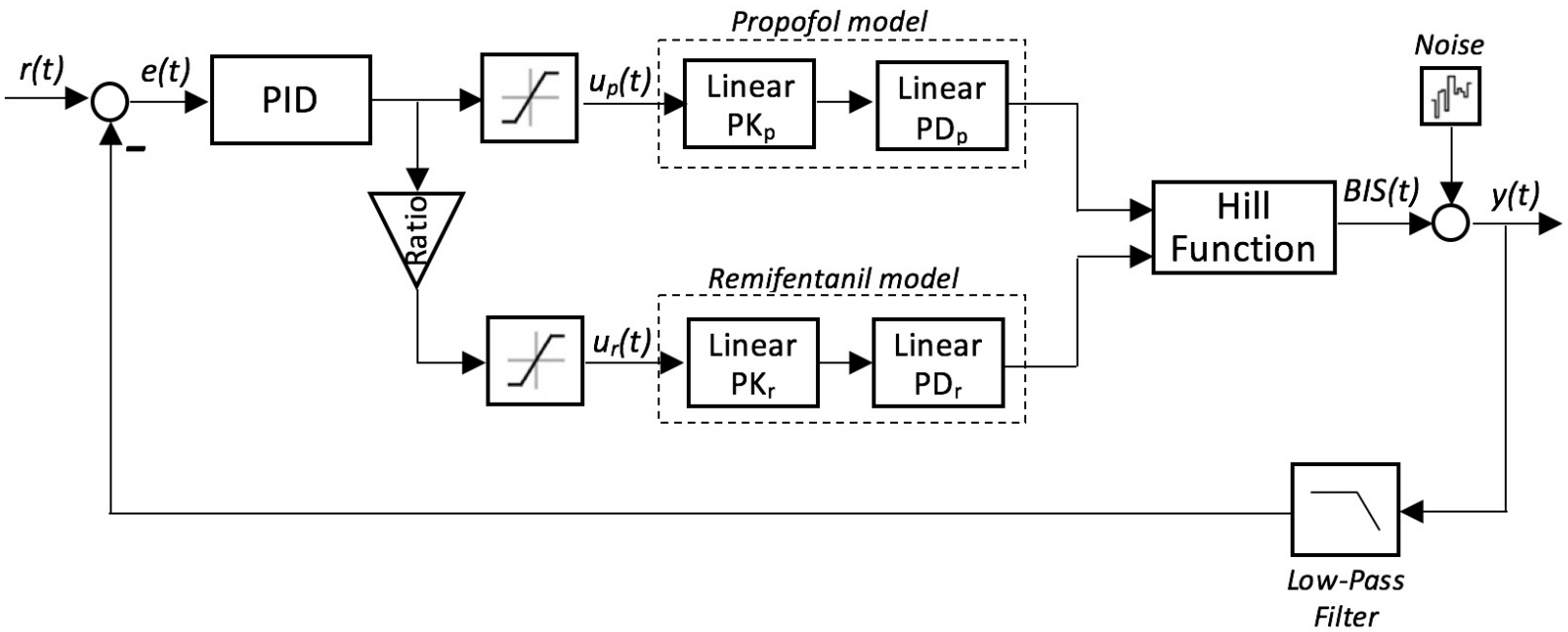
Two inputs: hypnotic (propofol) and analgesic (remifentanil)

One output: BIS

The extra degree of freedom of the MISO setting is dealt by explicitly fixing the ratio between the two drugs

The anesthesiologist select the opioid-hypnotic balance in the wide range [0.5 15]

Standard Proportional-Integral-Derivative (PID) controller: simple, well-understood



Optimal tuning

$$PID(s) = K_p \left(1 + \frac{1}{T_i s} + T_d\, s\right).$$

A min-max optimization problem

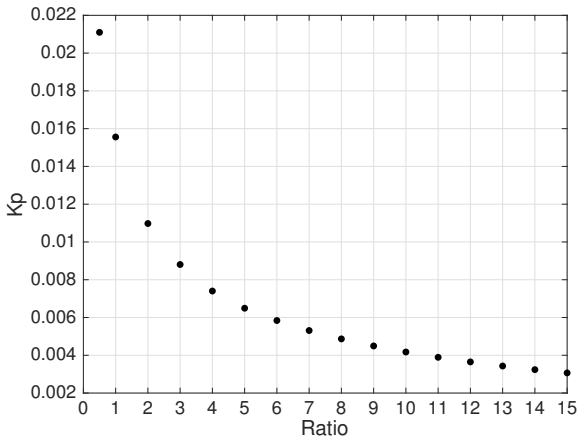
For each ratio in the range [0.5 15] we solve the optimization problem:

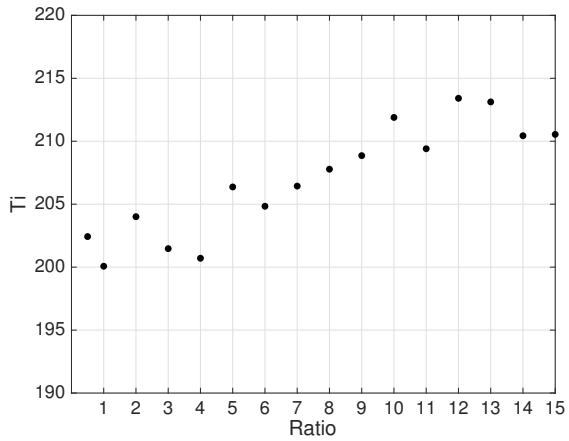
$$\min_{K_p, T_i, T_d} \max_{k \in \{1,\ldots,13\}} J_k(K_p, T_i, T_d)$$

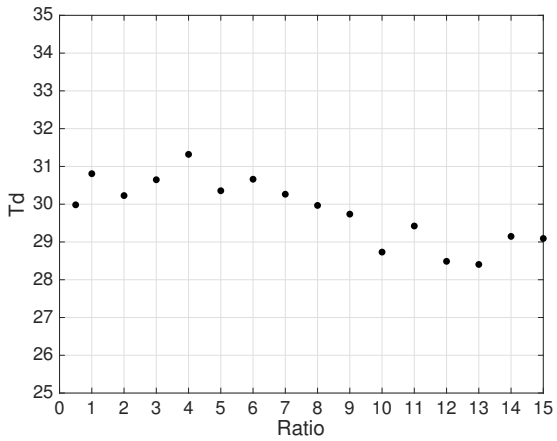
$$J_k(K_p, T_i, T_d) = \int_0^\infty |BIS_k(t) - 50|$$

Minimizing the Integrated Absolute Error (IAE): common in process control, yields **low overshoot and fast settling time**

Optimal parameters







$$CV := \frac{\sigma}{|\mu|} 100[\%]$$

$$CV_{K_p} = 69.40[\%] \qquad CV_{T_i} = 5.24[\%] \qquad CV_{T_d} = 7.41[\%]$$

Optimal time constants nearly invariant to w.r.t. propofol/remifentanil ratio!

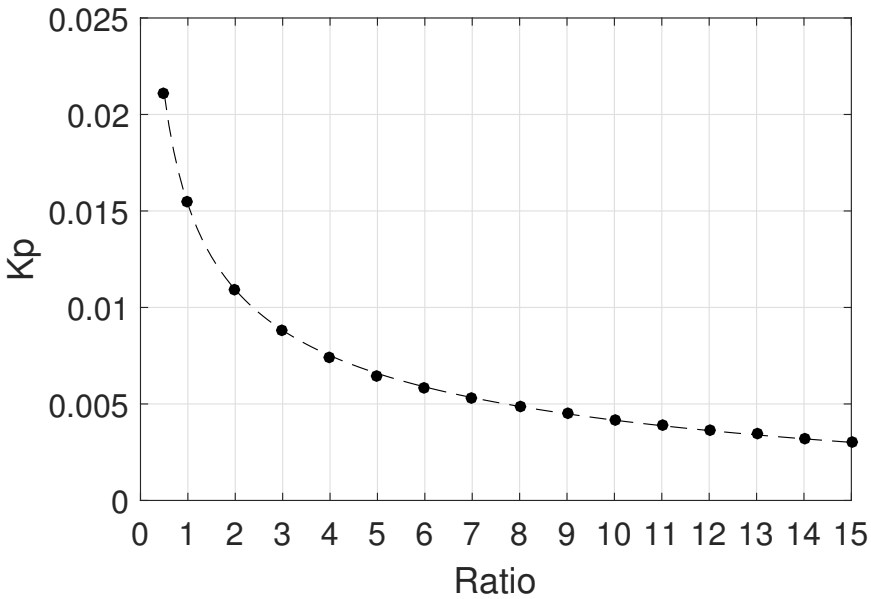
(Sub)optimal parameters

A new optimization problem

For each ratio in the range [0.5 15]

$$\min_{K_p} \max_{k\in\{1,\dots,13\}} J_k(K_p)$$

subject to $T_i = 206.98$ and $T_d = 29.83$.



Parameter	Set-point	Disturbance
K_p	$0.053 \cdot (ratio)^{-0.35} - 0.013$	$0.019 \cdot (ratio)^{-0.38} - 0.0040$
T_i	206.98	164.02
T_d	29.83	15.30

gain scheduling!

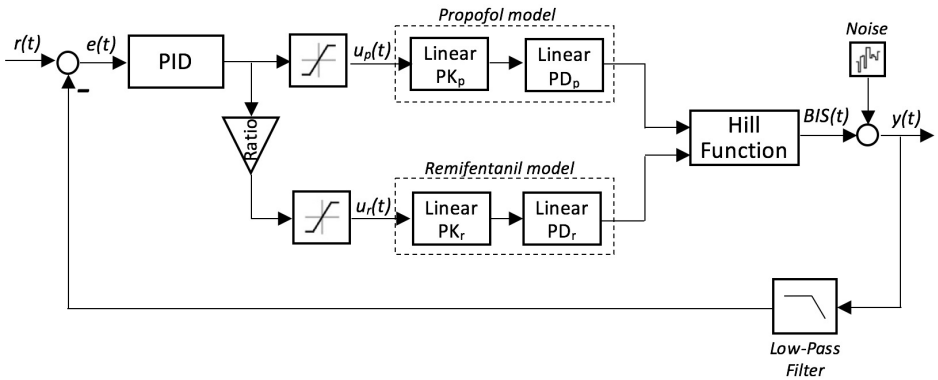
Low pass filter: performance decay ratio

$$PDR = \max_{k\in\{1,\dots,13\}} \frac{IAE_{filter,k} - IAE_k}{IAE_k},$$

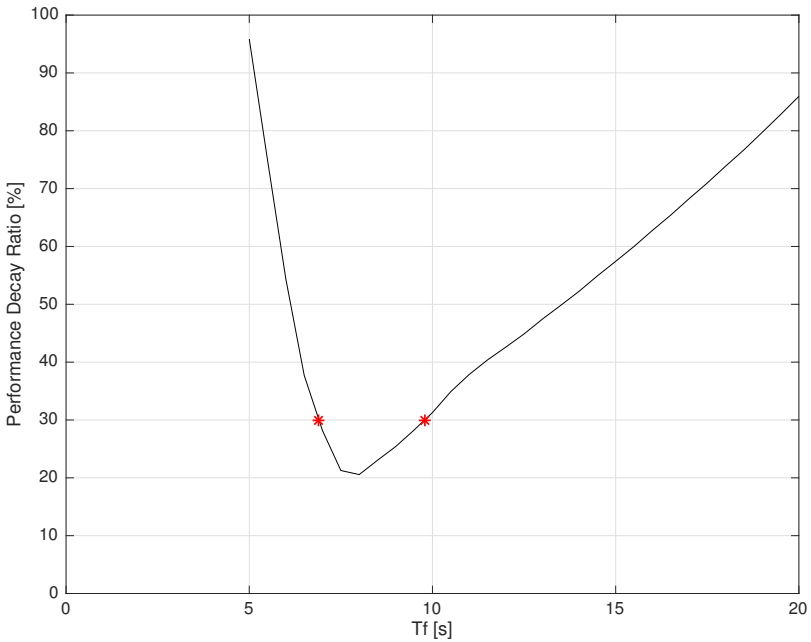
$IAE_{filter,k}$ IAE obtained with noise and filter

IAE_k ideal IAE obtained in the noise-free case with no filter

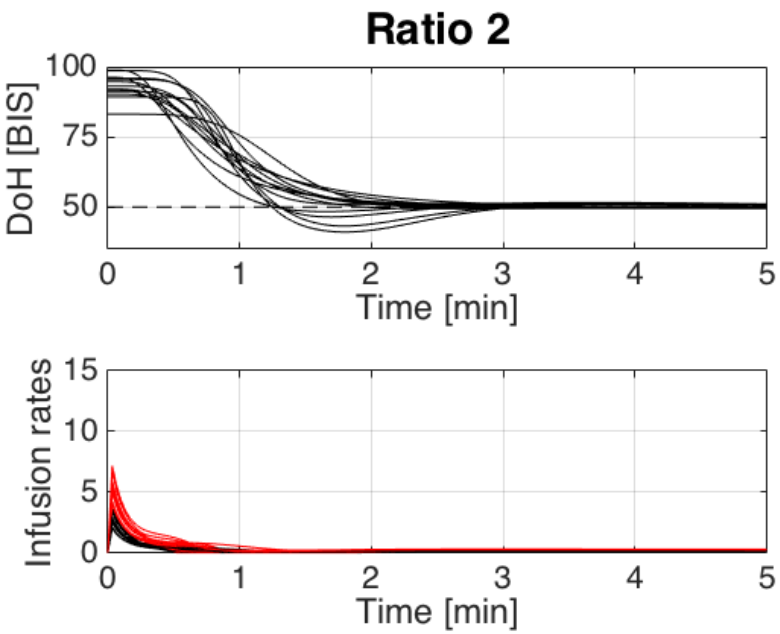
Performance decay ratio based tuning: $PDR = 30\%$

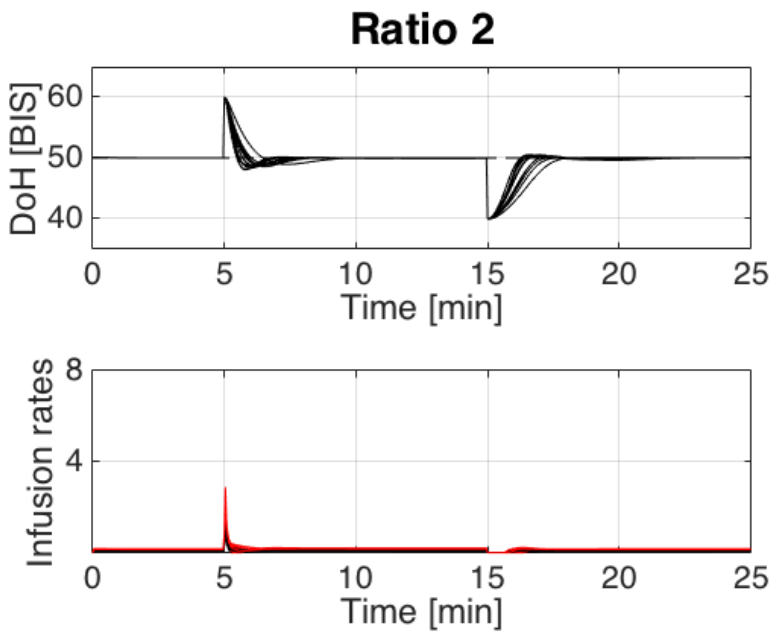


$$F(s) = \frac{1}{(T_f s + 1)^2}$$



PID control scheme for Propofol and Remifentanil





- The proposed solution satisfies the clinical specifications;
- The proposed control architecture allows the anesthesiologist to control the opioid-hypnotic balance during surgery through the selection of the ratio between drugs infusions

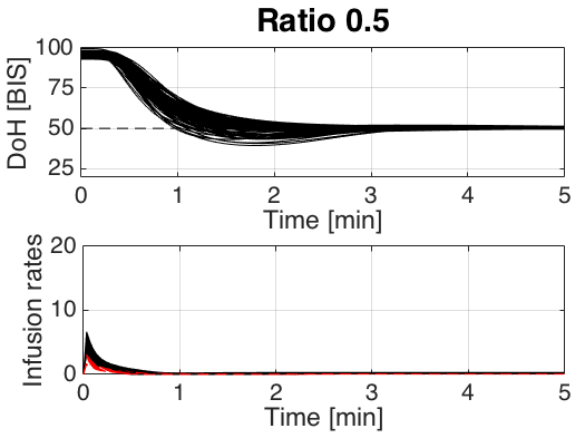
Performance indices

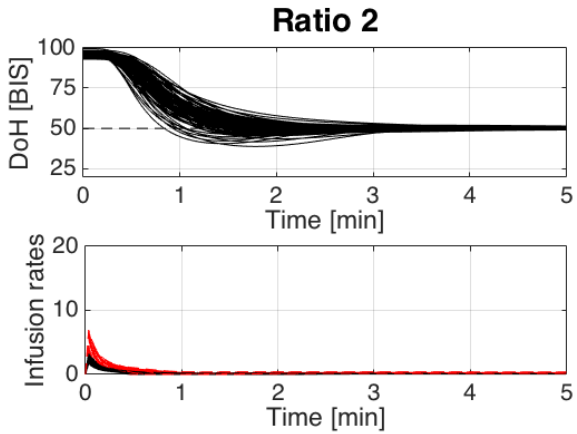
- TT observed time-to-target: time (in seconds) required for reaching the first time the target interval of 45-55 BIS values
- $BIS\text{-}NADIR$: the lowest BIS value reached during the induction phase
- $ST10$: settling time, time interval to reach and remain in the BIS range [45, 55] (that is, the target value of 50 ± 5)
- $ST20$: the same of $ST10$, but for a BIS range [40, 60]
- US: undershoot, defined as the amount of which the BIS exceeds the lower limit of the of 45

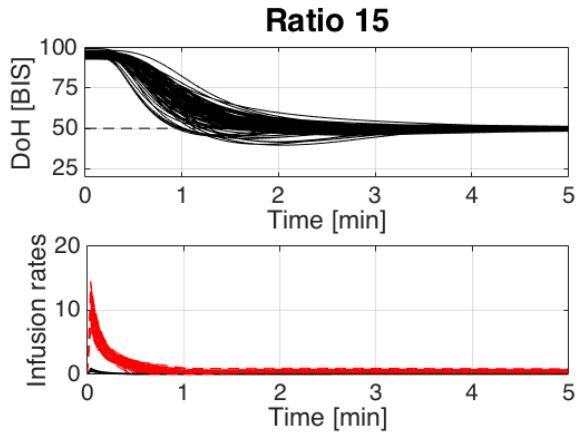
Performance indices

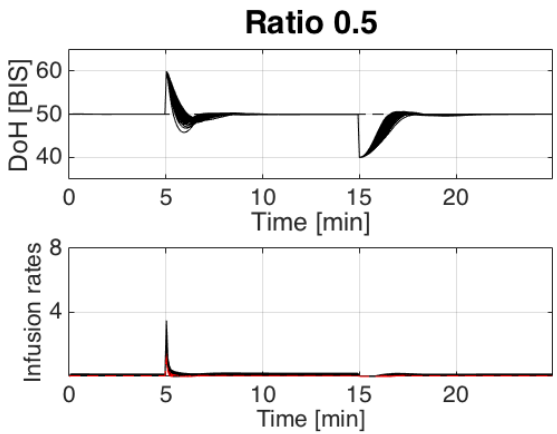
Ratio	TT $[min]$			*BIS-NADIR*			$ST10$ $[min]$			$ST20$ $[min]$			*US*		
	mean	min	max	mean	min	max	mean	min	max	mean	min	max	mean	min	max
0.5	1.43	1.17	1.87	48.48	42.88	50.43	1.58	1.17	2.26	1.19	0.94	1.61	0.29	0.00	2.12
1	1.41	1.01	1.80	48.21	41.40	49.95	1.58	1.01	2.37	1.17	0.85	1.48	0.42	0.00	3.60
2	1.41	0.98	1.88	48.11	41.04	50.15	1.58	0.98	2.39	1.17	0.83	1.50	0.44	0.00	3.96
3	1.43	1.05	1.92	48.36	42.07	50.27	1.59	1.05	2.32	1.18	0.88	1.57	0.35	0.00	2.93
4	1.45	1.12	1.97	48.56	43.31	50.40	1.59	1.12	2.22	1.19	0.93	1.64	0.23	0.00	1.69
5	1.44	1.06	2.00	48.50	43.38	50.33	1.59	1.06	2.17	1.19	0.94	1.67	0.21	0.00	1.62
6	1.43	1.00	2.01	48.36	42.79	50.11	1.58	1.00	2.24	1.18	0.90	1.68	0.23	0.00	2.21
7	1.43	0.96	2.03	48.25	42.34	49.95	1.57	0.96	2.28	1.17	0.87	1.68	0.24	0.00	2.66
8	1.42	0.93	2.05	48.19	41.98	49.75	1.62	1.22	2.32	1.17	0.84	1.69	0.28	0.00	3.02
9	1.42	0.91	2.08	48.14	41.76	49.75	1.62	1.22	2.34	1.17	0.82	1.69	0.33	0.00	3.24
10	1.42	0.89	2.10	48.11	41.49	49.80	1.58	1.21	2.36	1.16	0.81	1.70	0.41	0.00	3.51
11	1.42	0.88	2.12	48.12	41.34	49.86	1.58	1.20	2.38	1.16	0.80	1.70	0.46	0.00	3.66
12	1.41	0.86	2.13	48.09	41.13	49.93	1.59	1.19	2.40	1.16	0.79	1.70	0.52	0.00	3.87
13	1.42	0.85	2.15	48.08	41.05	50.00	1.59	1.18	2.41	1.16	0.78	1.71	0.55	0.00	3.95
14	1.42	0.85	2.17	48.06	40.94	50.05	1.60	1.17	2.42	1.16	0.77	1.71	0.59	0.00	4.06
15	1.41	0.84	2.18	48.03	40.79	50.11	1.60	1.16	2.43	1.16	0.76	1.71	0.63	0.00	4.21

Robustness


Ratio 0.5
DoH [BIS]
Time [min]
Infusion rates
Time [min]


Ratio 2
DoH [BIS]
Time [min]
Infusion rates
Time [min]


Ratio 15
DoH [BIS]
Time [min]
Infusion rates
Time [min]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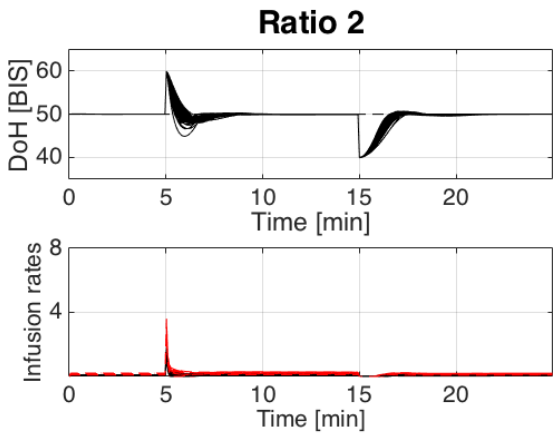
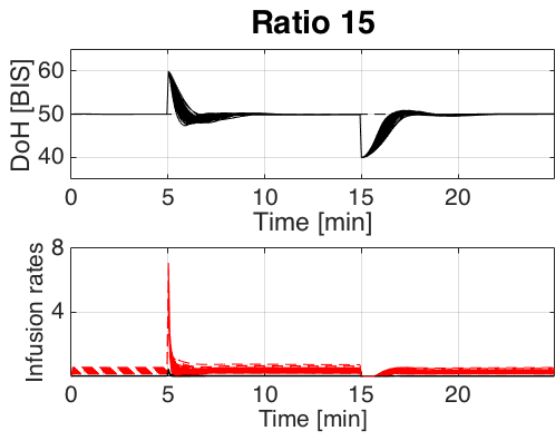
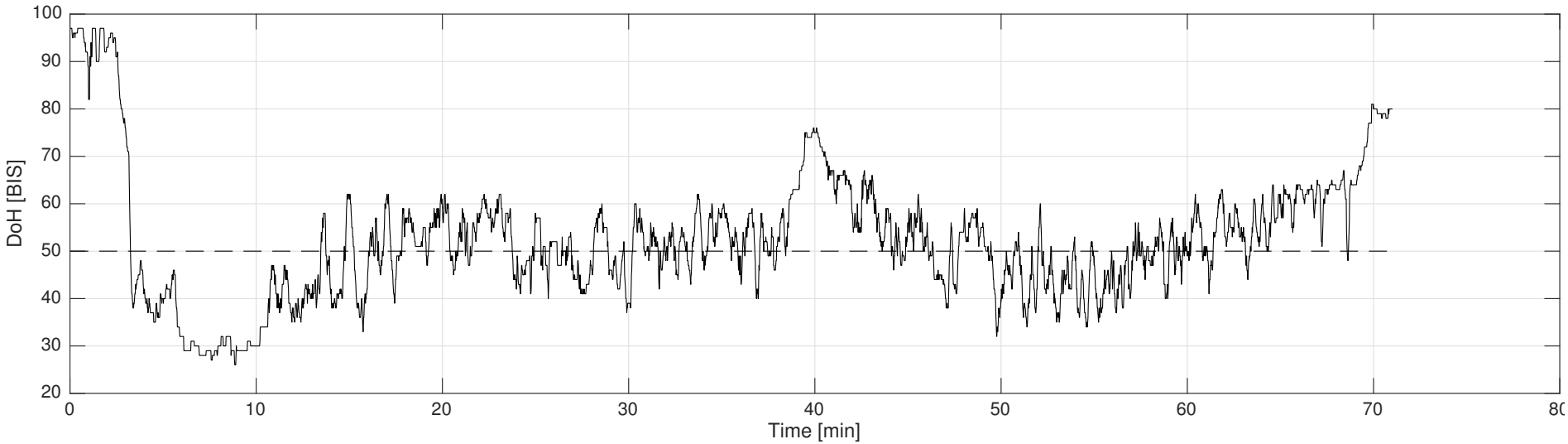
DoH [BIS]
Time [min]
Infusion rates
Time [min]


Ratio 2
DoH [BIS]
Time [min]
Infusion rates
Time [min]


Ratio 15
DoH [BIS]
Time [min]
Infusion rates
Time [min]

Event-based control



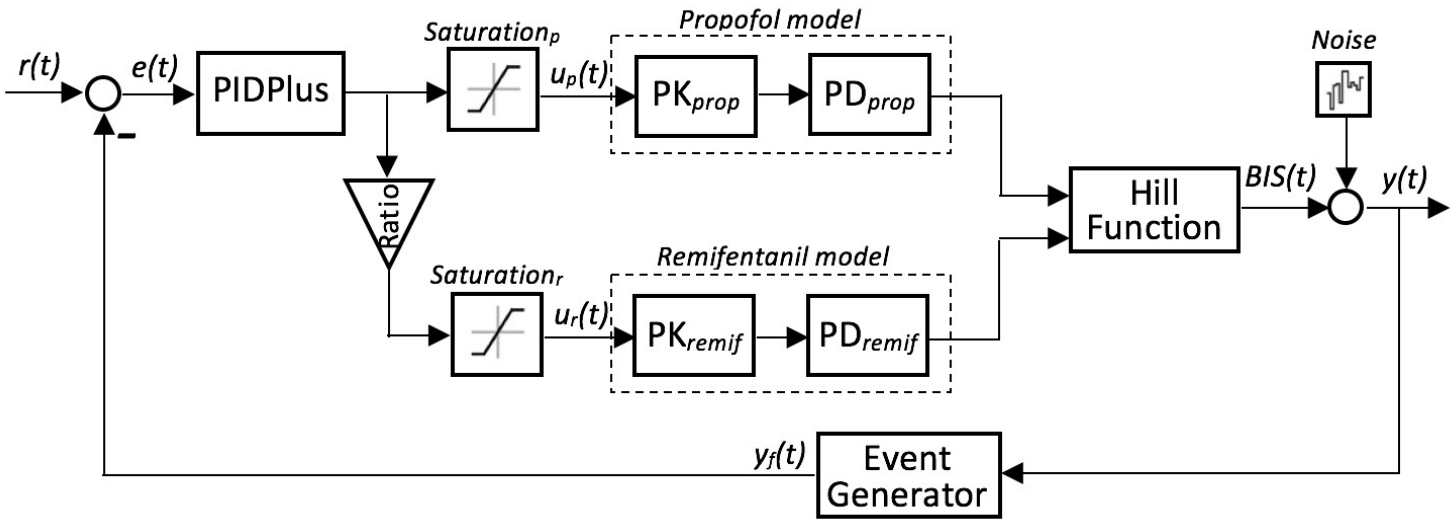
We do no want to react to noise and artifacts in the BIS signal

A control action that changes less frequently is better perceived by clinical practitioners

Only update the control action when it is really necessary

An **event** triggers the update

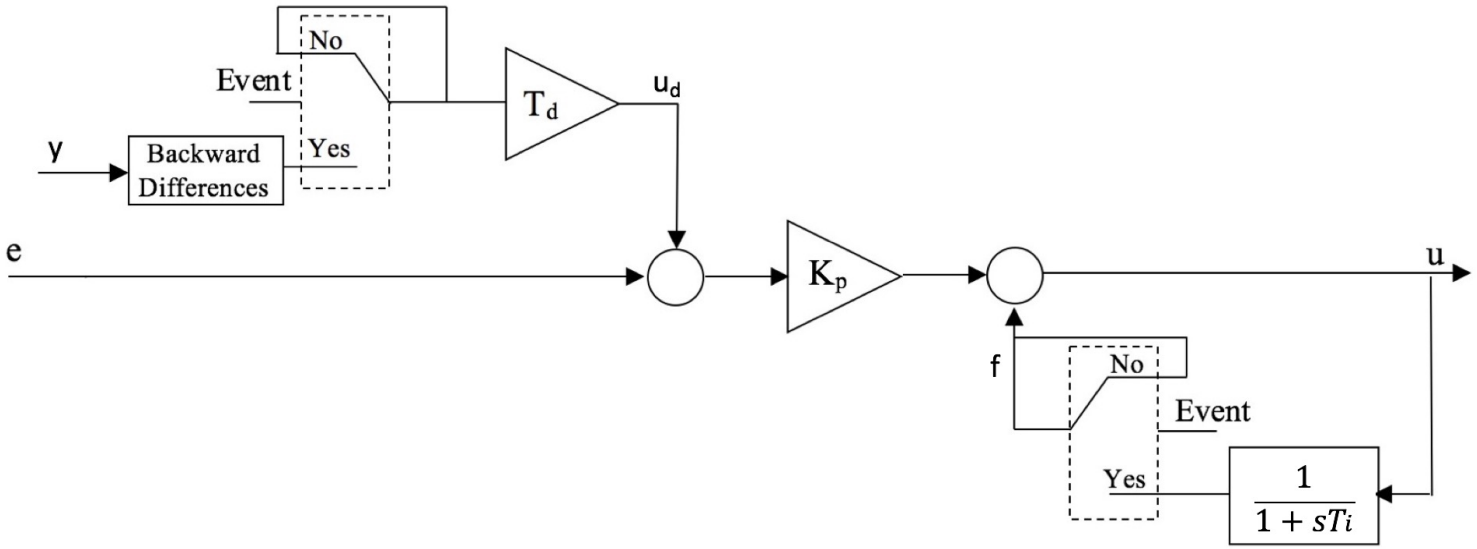
Event-based control architecture



Event generator generate and event when a certain condition becomes true, and send data to the controller. One parameter Δ_i

PIDPlus is a generalization of the PID controller for event-sampled control systems. Three parameters: K_p, T_i, and T_d

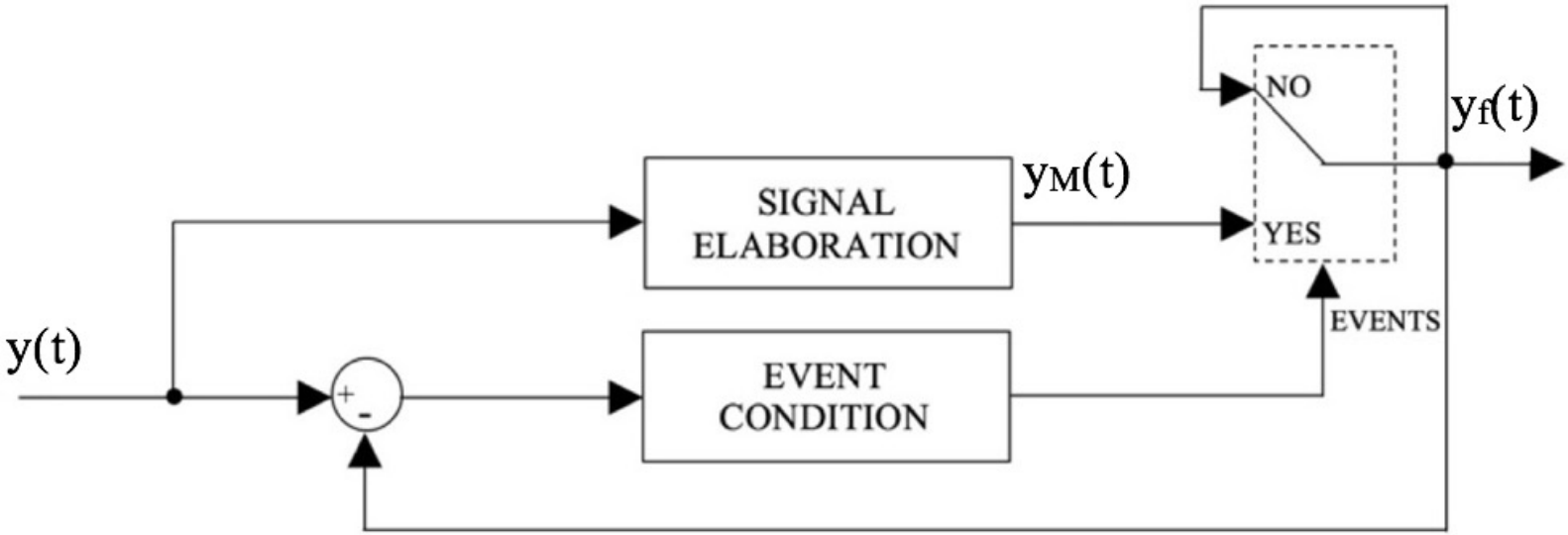
PIDPlus controller



Remark

The PIDPlus controller is typically associated to a standard send-on-delta technique $|y(t) - y(t_{last})| \leq \Delta_i$

Event generator



Event generator

- Event generation condition

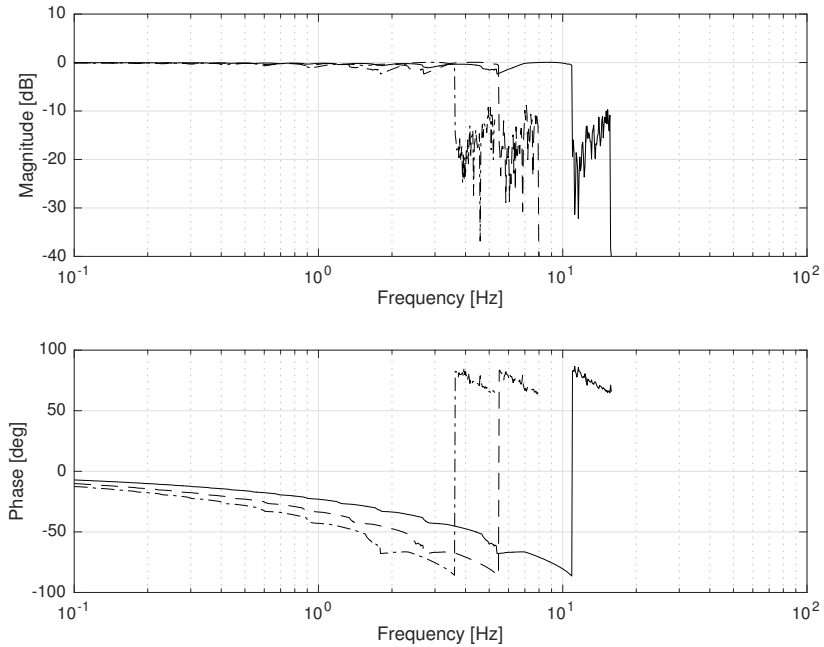
$$E.C. = \left| \int_{t_{last}}^{t} y(t) - y_c(t_{last}) dt \right| > \Delta_i$$

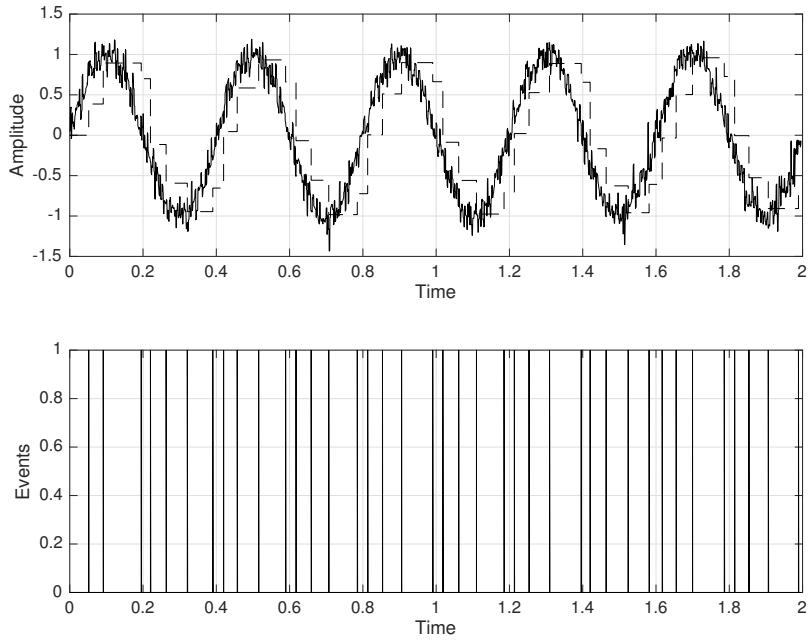
- Δ_i allows the user to increase or reduce the variation in the signal that is necessary to generate an event
- Signal elaboration

$$y_M(t) = \frac{\int_{t_{last}}^{t} y(t) dt}{t - t_{last}}$$

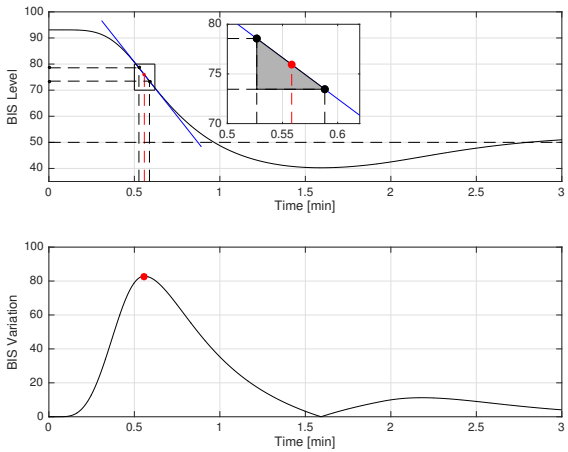
- The noise is filtered because of the double integration

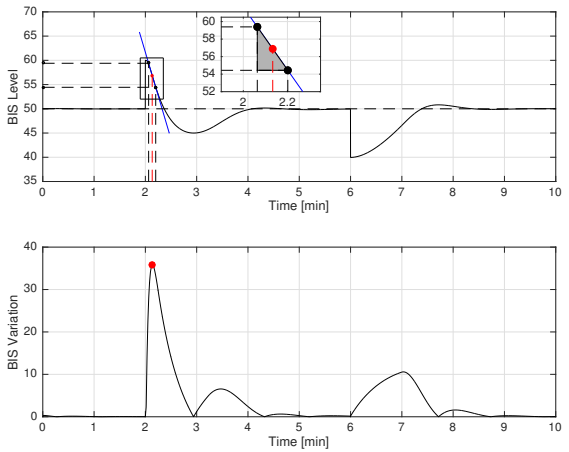
Event generator: Δ_i





Tuning



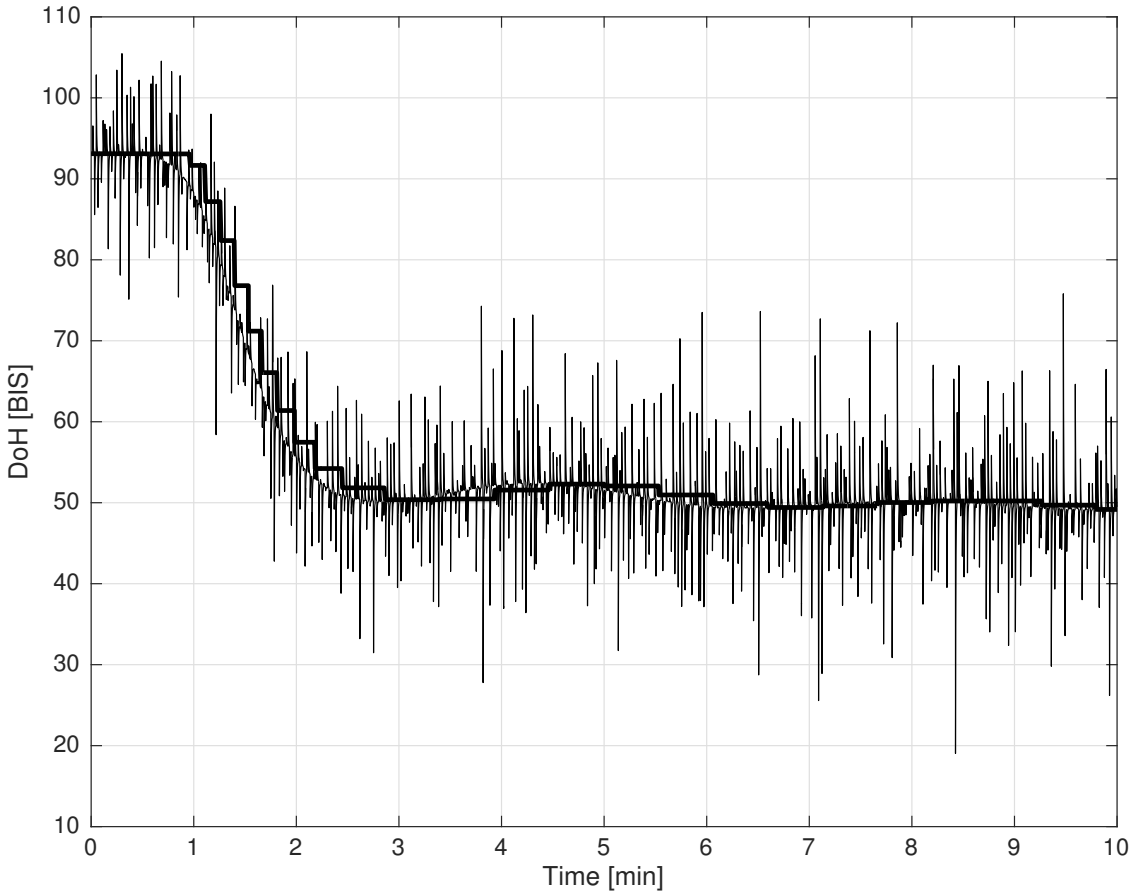


- **Event generator tuning:** a BIS variation grater than 5 is always detected
- **PIDPlus tuning:** same min-max optimization problem plus gain scheduling

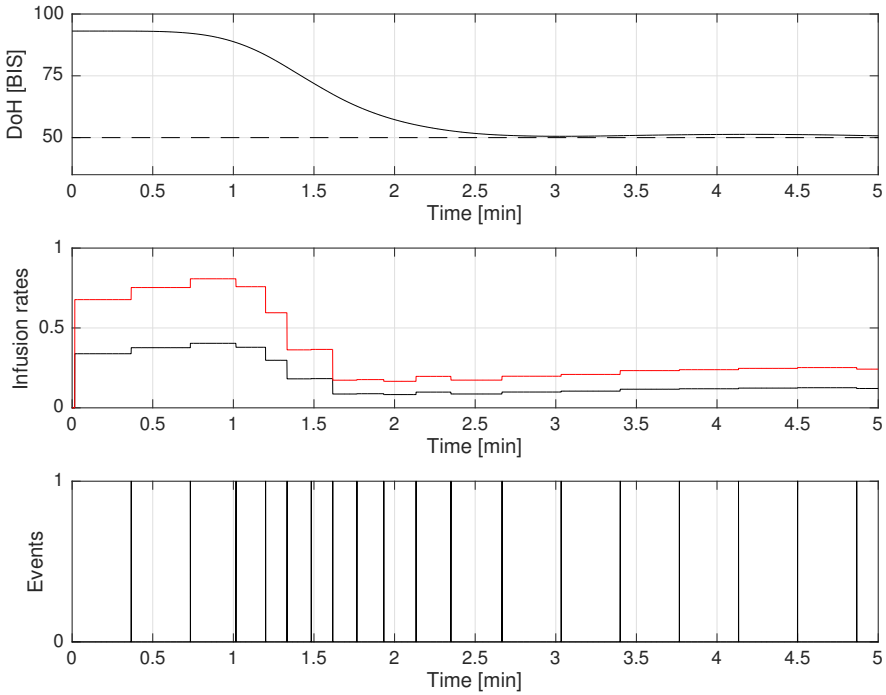
$$\min_{K_p,T_i,T_d} \max_{k\in\{1,\ldots,13\}} IAE(K_p,T_i,T_d)$$

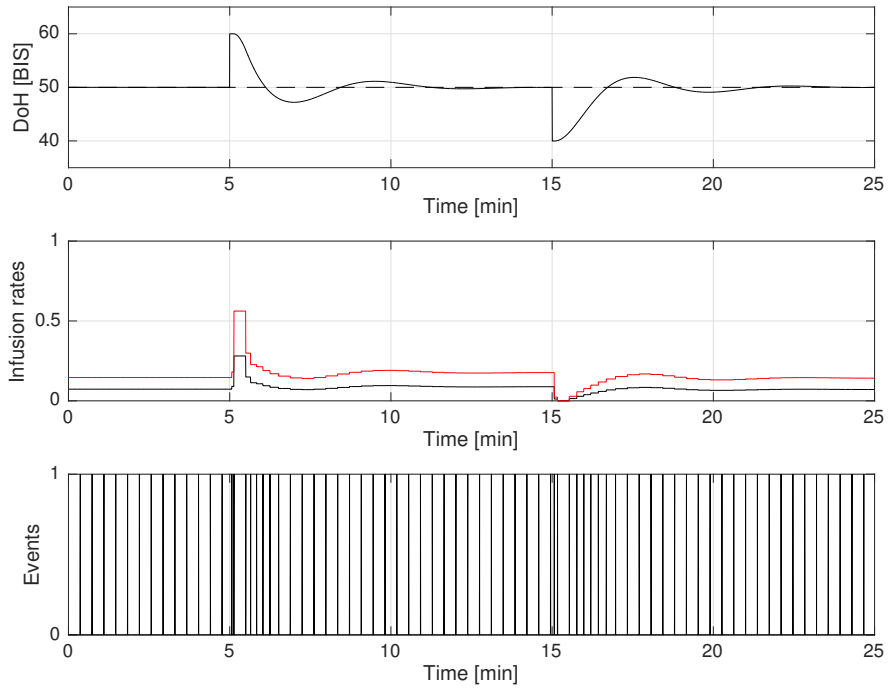
Parameter	Set-point	Disturbance
K_p	0.0053	0.0057
T_i	174.4027	201.0373
T_d	17.2538	2.8949
Δ_i	47.1233	12.2183

Simulation Results - Noise cancellation



Simulation Results - Average Patient





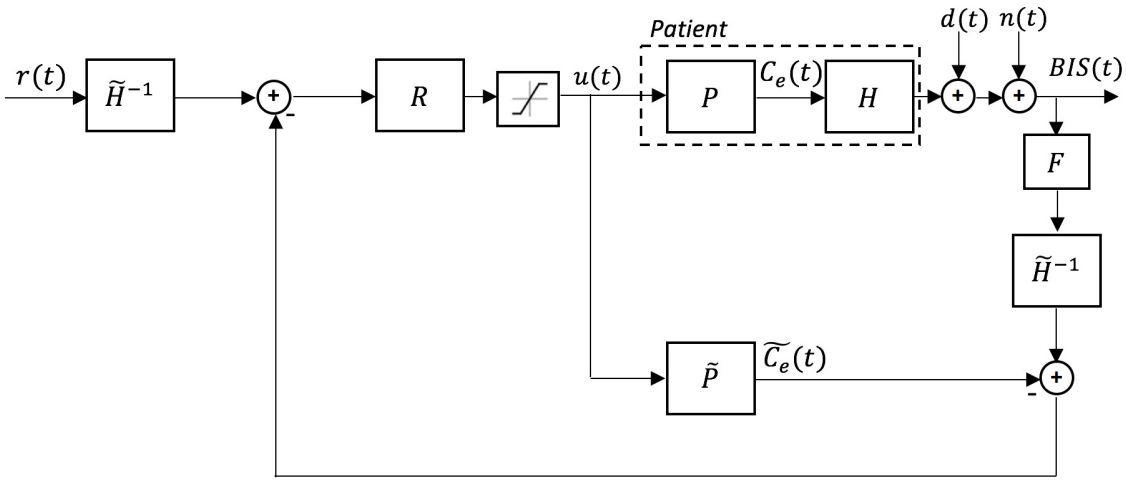
Performance indices

Ratio	TT [min]			BIS NADIR			ST10 [min]			ST20 [min]			US		
	mean	min	max	**mean**	min	max	**mean**	min	max	**mean**	min	max	**mean**	min	max
0.5	**2.00**	1.76	2.41	**48.35**	44.33	49.44	**2.06**	1.76	2.61	**1.76**	1.53	2.21	**0.05**	0.00	0.67
1	**2.06**	1.77	2.44	**48.39**	44.32	49.35	**2.12**	1.77	2.61	**1.81**	1.48	2.15	**0.05**	0.00	0.68
2	**2.07**	1.73	2.53	**48.34**	44.33	49.40	**2.13**	1.73	2.61	**1.81**	1.46	2.19	**0.05**	0.00	0.67
3	**2.04**	1.75	2.51	**48.39**	44.33	49.34	**2.10**	1.75	2.61	**1.79**	1.48	2.21	**0.05**	0.00	0.67
4	**1.99**	1.68	2.49	**48.34**	44.34	49.43	**2.10**	1.68	2.60	**1.75**	1.49	2.22	**0.06**	0.00	0.66
5	**1.95**	1.60	2.48	**48.47**	44.39	49.51	**2.07**	1.60	2.57	**1.71**	1.45	2.21	**0.09**	0.00	0.61
6	**1.96**	1.57	2.51	**48.41**	44.34	49.37	**2.08**	1.57	2.59	**1.71**	1.42	2.21	**0.10**	0.00	0.66
7	**1.95**	1.52	2.54	**48.45**	44.46	49.34	**2.18**	1.75	2.97	**1.69**	1.37	2.19	**0.08**	0.00	0.54
8	**1.94**	1.47	2.56	**48.47**	43.83	49.53	**2.17**	1.72	2.86	**1.68**	1.34	2.21	**0.16**	0.00	1.17
9	**1.93**	1.42	2.58	**48.46**	43.97	49.49	**2.17**	1.70	2.92	**1.66**	1.30	2.18	**0.13**	0.00	1.03
10	**1.95**	1.41	2.62	**48.48**	44.12	49.48	**2.18**	1.69	2.92	**1.67**	1.29	2.19	**0.09**	0.00	0.88
11	**1.97**	1.38	2.65	**48.44**	44.09	49.44	**2.20**	1.70	2.86	**1.66**	1.26	2.15	**0.11**	0.00	0.91
12	**1.98**	1.36	2.68	**48.41**	44.10	49.38	**2.21**	1.70	2.83	**1.66**	1.25	2.15	**0.10**	0.00	0.90
13	**1.97**	1.38	2.71	**48.51**	44.37	49.42	**2.15**	1.70	2.84	**1.67**	1.26	2.20	**0.05**	0.00	0.63
14	**2.00**	1.33	2.75	**48.31**	43.78	49.36	**2.24**	1.68	2.84	**1.66**	1.22	2.15	**0.11**	0.00	1.22
15	**2.00**	1.35	2.75	**48.48**	44.43	49.41	**2.17**	1.69	2.83	**1.68**	1.24	2.20	**0.04**	0.00	0.57

- the event-based control action “mimics” the anesthesiologists and is better accepted by clinical practitioner
- the controller is robust, same controller can be used for any patient
- the noise is almost completely canceled: less stress for the actuator
- we are only partially exploiting the information that we have on the patient

Model-based control for Propofol

We exploit all the information from the patient demographics



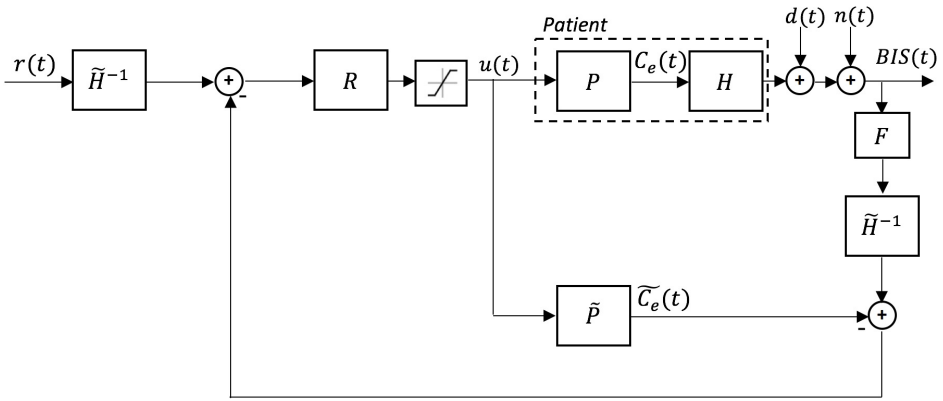
P and $\tilde{H}$: real patient linear dynamic and Hill function

$\tilde{P}$: nominal linear dynamic of patient (depend on demographics)

$\tilde{H}^{-1}$: inverse of the average Hill function

Only the difference between the nominal response and the real one is fed back to the controller

Model-based control for Propofol



$$
\begin{aligned}
\dot{q}_1(t) &= -(k_{10}+k_{12}+k_{13})q_1(t) \\
&\quad +k_{21}q_2(t)+k_{31}q_3(t)+u(t) \\
\dot{q}_2(t) &= k_{12}q_1(t)-k_{21}q_2(t) \\
\dot{q}_3(t) &= k_{13}q_1(t)-k_{31}q_3(t) \\
\dot{C}_e(t) &= k_{1e}C_p(t)-k_{e0}C_e(t)
\end{aligned}
$$

$$
P(s) = K\frac{\left(1+\frac{s}{z_1}\right)\left(1+\frac{s}{z_1}\right)}{\left(1+\frac{s}{p_1}\right)\left(1+\frac{s}{p_2}\right)\left(1+\frac{s}{p_3}\right)}\cdot\frac{k_{e0}}{s+k_{e0}}
$$

$$
R(s) = P^{-1}(s)\cdot\frac{1}{(\lambda_1 s+1)(\lambda_2 s+1)}
$$

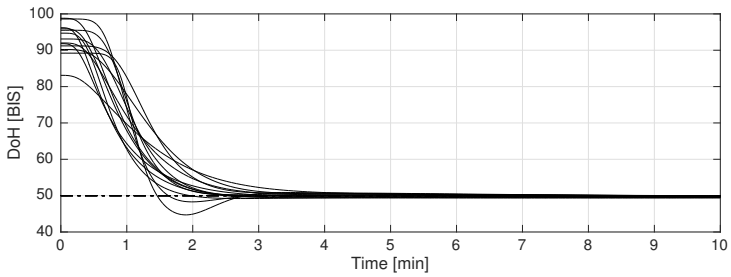
Controller tuning

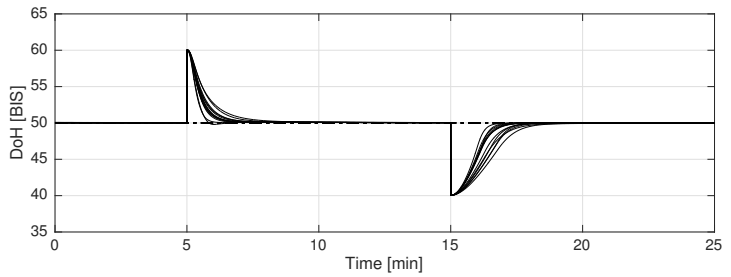
$$
\min_{\lambda_1,\lambda_2}\ \max_{k\in\{1,\ldots,13\}} J_k(\lambda_1,\lambda_2)
$$

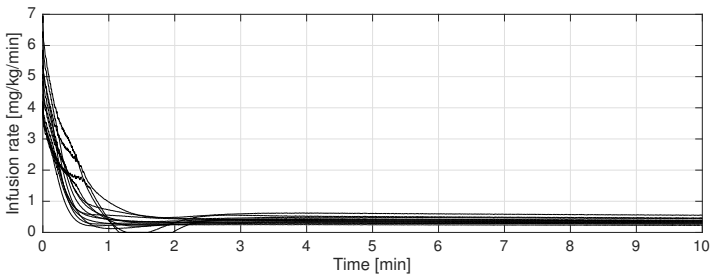
Parameter	Set-point	Disturbance
λ_1	0.0524	0.0372
λ_2	0.0524	0.0372

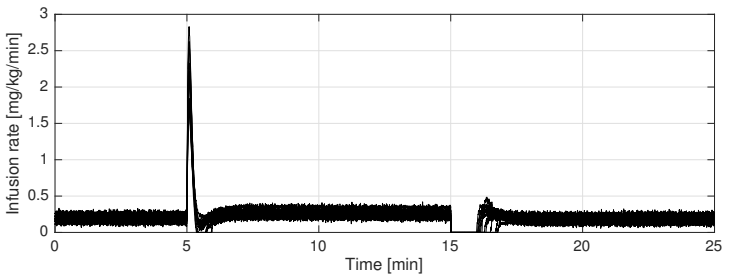
The optimal controller has coincident poles

The filter is tuned by using the performance decay ratio









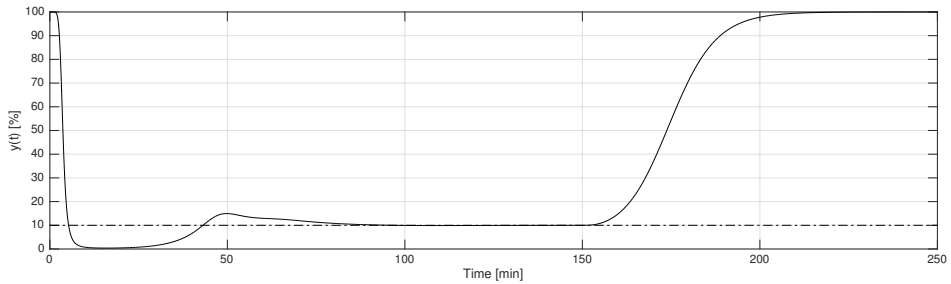
Individualized medicine

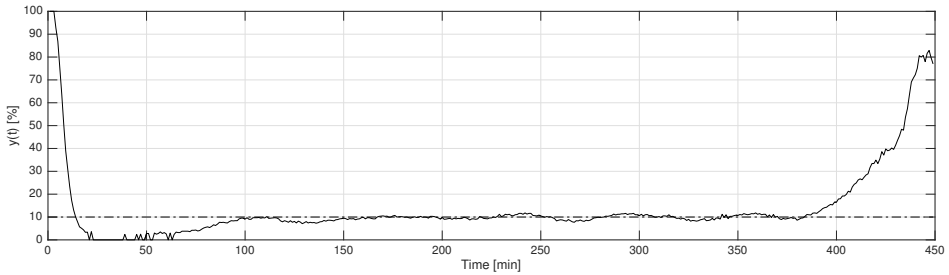
The patient model integrated in the control architecture provides a personalized infusion profile

Neuromuscolar blockade

Control requirements:

- A bolus provides the infusion phase;
- Fast set-point tracking (y(t)=10%);
- Bounded oscillations during maintenance phase ;
- Robustness to intra-patient variability;
- Robustness to inter-patient variability.

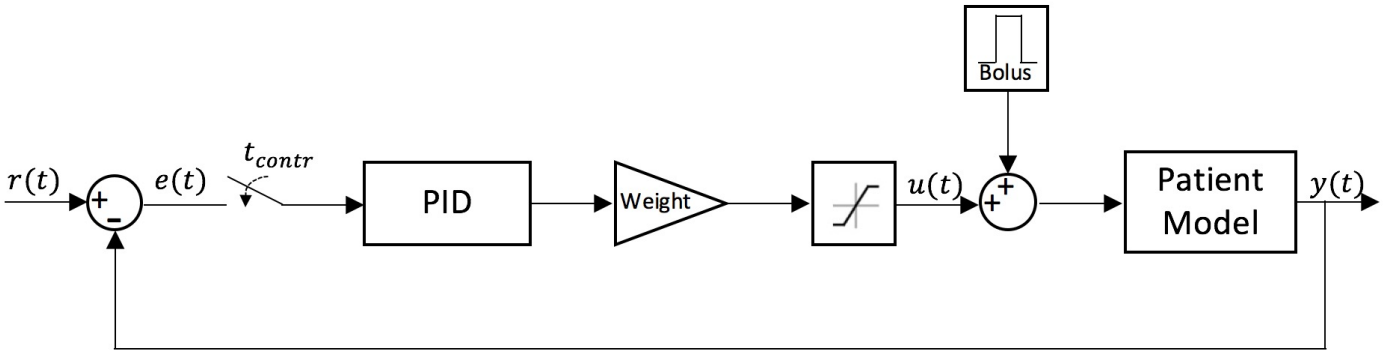




Design of the complete control structure → Tuning with optimization method **(GA/PSO)** → Control robustness validated on models from **real data**

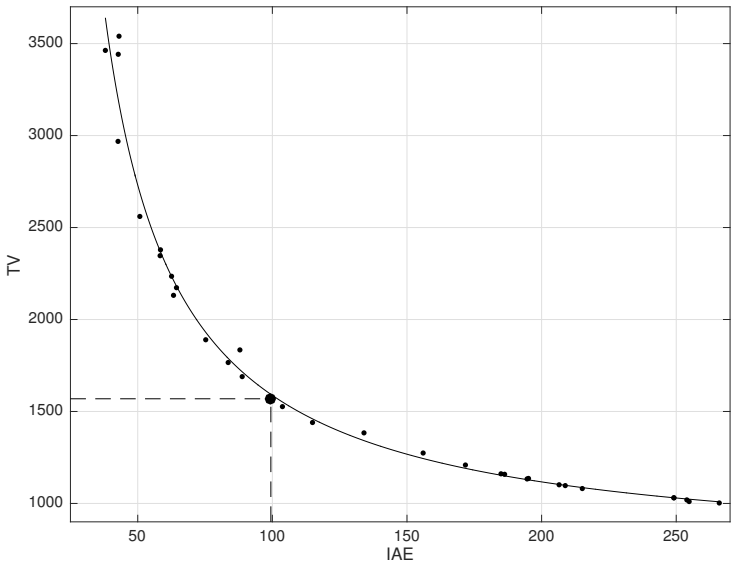
PID control scheme for Atracurium

A **PID control scheme** for the regulation of the NMB level is proposed by considering the atracurium infusion as control variable and the Train-Of-Four (TOF) signal as feedback.

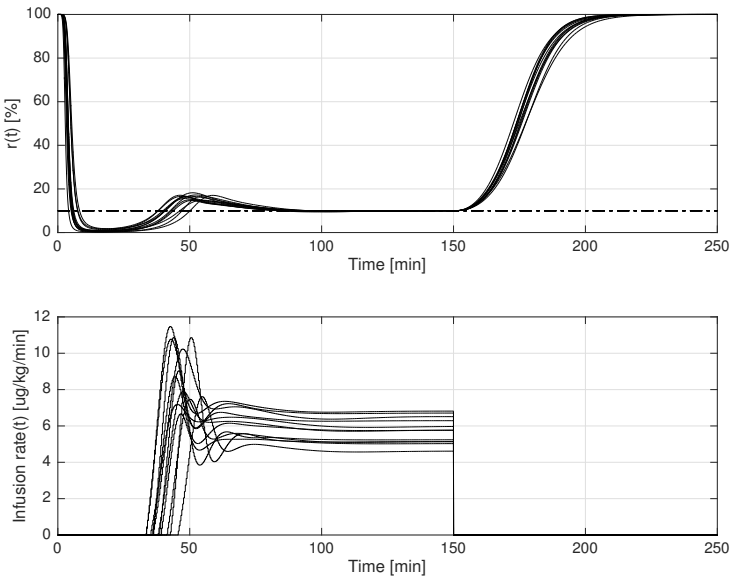


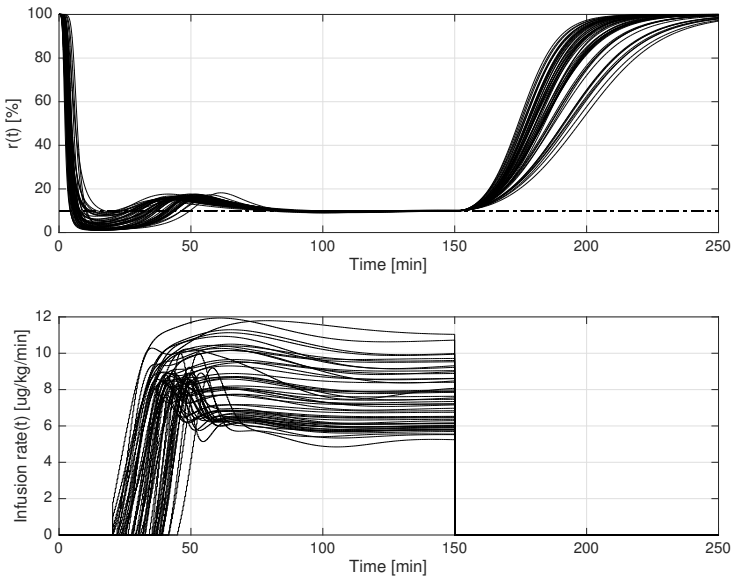
$$\min_{k_p,T_i,T_d} \max_{k\in\{1,\dots,12\}} J_k(K_p,T_i,T_d;\lambda) \qquad (1)$$

$$J(\lambda) = IAE + \lambda\, TV \qquad (2)$$



PID control scheme for Atracurium

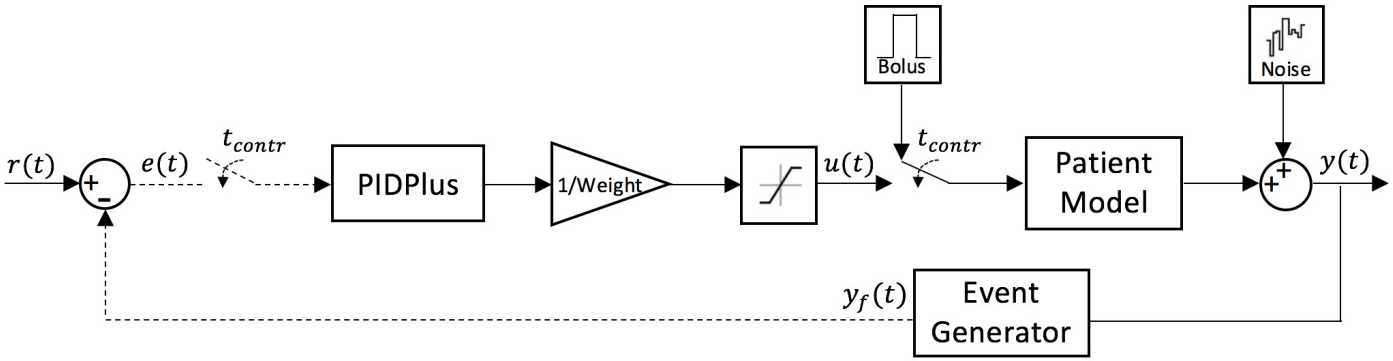




- Simulation results have shown that the methodology guarantees a satisfactory performance.
- The controller provides the required inter-patient robustness in spite of the simplicity of the control architecture.

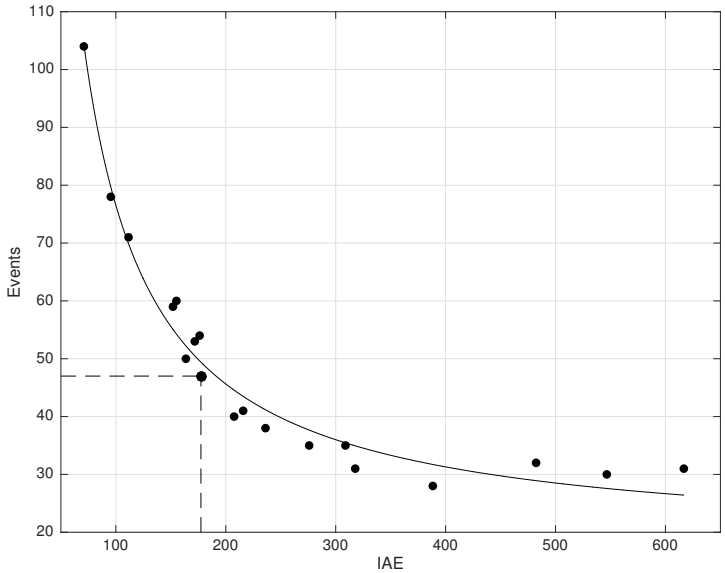
Event-based control for Atracurium

An **event-based approach** to the NMB control problem is proposed.

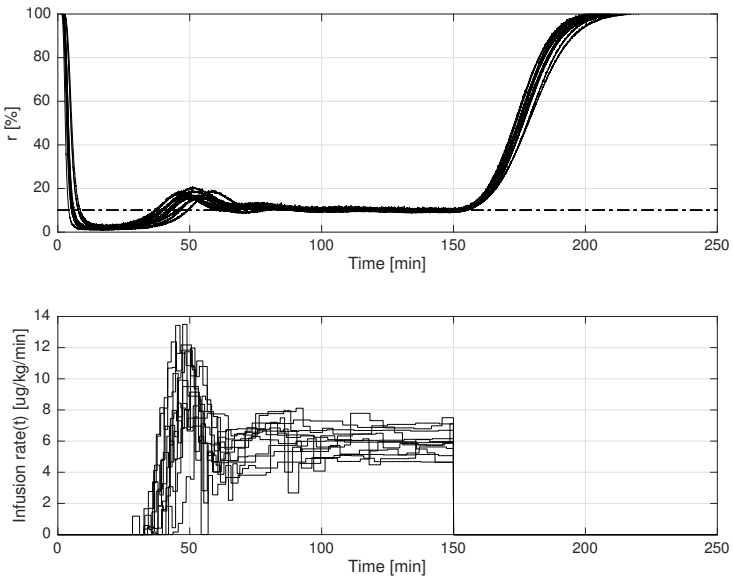


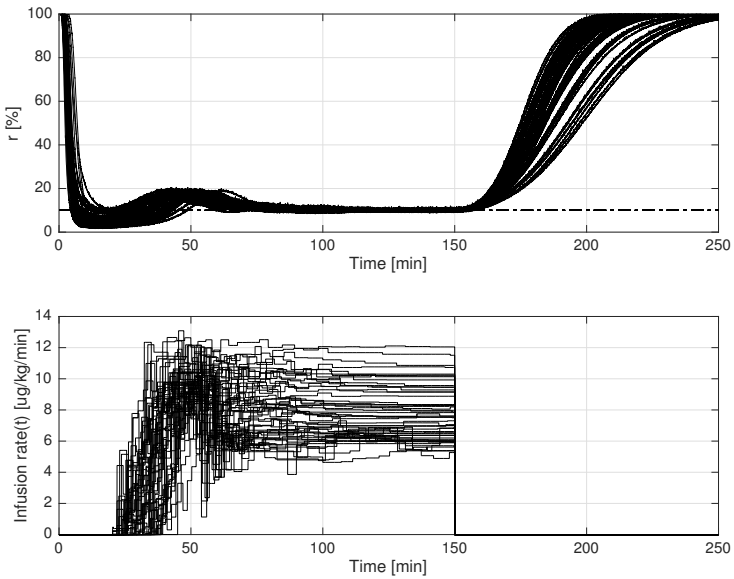
$$\min_{K_p,T_i,T_d,\Delta_i} \max_{k\in\{1,\ldots,12\}} J_k(K_p, T_i, T_d, \Delta_i; \lambda) \qquad (3)$$

$$J(\lambda) = IAE + \lambda\, NE \qquad (4)$$



Event-based control for Atracurium





- Simulation results have shown that the methodology guarantees a satisfactory performance.
- The controller provides the required inter-patient robustness in spite of the simplicity of the control architecture.
- Event-based control advantages.

Conclusions

- There are *clear benefits* deriving from the automatic regulation of clinical anesthesia
- Even small improvements can potentially have a major economical impact
- Stable anesthesia is beneficial for the patient and for the anesthesiologist
- It is important to offer *clinically appealing* solution
- The ACTIVA 2 study has just started...

Selected references

- F. Padula, C. M. Ionescu, N. Latronico, M. Paltenghi, A. Visioli, and G. Vivacqua. *Inversion-based propofol dosing for intravenous induction of hypnosis.* Communications in Nonlinear Science and Numerical Simulation, 39:481-494, 2016.
- F. Padula, C. M. Ionescu, N. Latronico, M. Paltenghi, A. Visioli, and G. Vivacqua. *Optimized PID control of depth of hypnosis in anesthesia.* Computer Methods and Programs in Biomedicine, 144:21-35, 2017.
- L. Merigo, M. Beschi, F. Padula, N. Latronico, M. Paltenghi, A. Visioli, *Event-Based Control of Depth of Hypnosis in Anesthesia*, Computer Methods and Programs in Biomedicine, 147:63-83, 2017.
- L. Merigo, M. Beschi, F. Padula, A. Visioli, *A noise-filtering event generator for PIDPlus controllers*, Journal of the Franklin Institute, 355:774-802, 2018.
- L. Merigo, F. Padula, A. Pawlowski, S. Dormido, J. L. Guzmán Sánchez, N. Latronico, M. Paltenghi, and A. Visioli, *A model-based control scheme for depth of hypnosis in anesthesia* Biomedical Signal Processing and Control, 42:216-229, 2018.
- L. Merigo, M. Beschi, F. Padula, N. Latronico, M. Paltenghi, A. Visioli, *Optimized PID Control of Propofol and Remifentanil Coadministration for General Anesthesia*, Communications in Nonlinear Science and Numerical Simulation, 72:194-212, 2019.

Conference proceedings

F. Padula, C. M. Ionescu, N. Latronico, M. Paltenghi, A. Visioli, and G. Vivacqua. *A gain-scheduled PID controller for propofol dosing in anesthesia*. In Proceedings of the 9th IFAC Symposium on Biological and Medical Systems, Berlin (Germany), 2015.
L. Merigo, M. Beschi, F. Padula, A. Visioli, *A New Event Generator for PIPlus Control Systems*, 2nd international Conference, Event-Based Control, Communication and Signal Processing, Krakow (Poland), 2016.
L. Merigo, M. Beschi, F. Padula, N. Latronico, M. Paltenghi, A. Visioli, *Event Based Control of Propofol and Remifentanil Coadministration During Clinical Anesthesia*, 3rd international Conference, Event-Based Control, Communication and Signal Processing, Funchal, Madeira (Portugal), 2017.
A. Pawlowski, L. Merigo, J. L. Guzmán, A. Visioli, S. Dormido, *Event-based GPC for depth of hypnosis in anesthesia for efficient use of propofol*, 3rd international Conference, Event- Based Control, Communication and Signal Processing, Funchal, Madeira (Portugal), 2017.
L. Merigo, F. Padula, N. Latronico, T. Medonça, M. Paltenghi, P. Rocha Malonek and A. Visioli, *On the Identification of Propofol Effects on Anesthesia Using BIS Measurements*, 20th IFAC 2017 World Congress, Toulouse (France), 2017.
L. Merigo, M. Beschi, F. Padula, A. Visioli, *On the Tuning of a PIDPlus Control System with a Noise-filtering Event Generator*, 22nd IEEE International Conference on Emerging Technologies and Factory Automation, Limassol (Cyprus), 2017.
L. Merigo, F. Padula, N. Latronico, T. Mendonça, M. Paltenghi, P. Rocha, A. Visioli, *Optimized PID tuning for the automatic control of neuromuscular blockade* 3rd IFAC Conference on Advances in PID Control, Gent (Belgium), 2018.
A. Pawlowski, L. Merigo, J. L. Guzmán, S. Dormido, A. Visioli, *Two-degree-of-freedom control scheme for depth of hypnosis in anesthesia* 3rd IFAC Conference on Advances in Proportional-Integral-Derivative Control, Gent(Belgium), 2018.
L. Merigo, M. Beschi, F. Padula, N. Latronico, T. Mendonça, M. Paltenghi, A. Visioli, *Optimization of PIDPlus Control for Neuromuscular Blockade During General Anesthesia*, 4th International Conference on Event-Based Control, Communication and Signal Processing, Perpignan, France, 27-29 June 2018.
Z. Guo, A. Medvedev, L. Merigo, N. Latronico, M. Paltenghi, A. Visioli, *Synthetic Patient Database of Drug Effect in General Anesthesia for Evaluation of Estimation and Control Algorithms*, 18th IFAC Symposium on System Identification, Stockholm, Sweden, 9-11 July 2018.