Robust Control of Depth of Anesthesia of Patients Under Sedation based on $H_\infty$ design

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Abstract

This work presents a case study on the design of a robust controller for the level of hypnosis (DoA) for patients subject to general anesthesia, induced by the drug propofol. This process is represented by a linear model together with a non-parametric uncertainty description that is evaluated using a database with 20 patients undergoing sedation. By using $H_\infty$ methods, the controller ensures robust stability and performance for the class of patient models considered. The controller that results from this procedure is approximated by a controller with a lower order, that in turn is redesigned in discrete time, for computer control application. The resulting controller is evaluated in simulations made using a realistic nonlinear model of DoA.

1 Introduction

The administration of sedatives during general anesthesia is made in order to prevent patient awareness during the surgical procedure and induce hypnosis, also called depth of anesthesia (DoA). An aware state of the patient resulting from under-dosing may cause serious long-term psychological consequences. On the other hand, the overdosage may be harmful with respect to postoperative morbidity and mortality. So, the appropriate dosage of the sedative drug is an important issue for the patient well-being. The current anesthetic procedure to induce and maintain DoA is based on recommended dosages for the patient characteristics and on the anesthetist experience. The automatic control of DoA is now a possibility due to the use of the electroencephalogram signal, resulting in measures such as the bispectral index (BIS) [1], rather than the use of unmeasurable physiological reactions, such as the loss of eye lash and corneal reflex or the absence of movement in response to squeezing the trapezious muscle.

Several control techniques have been studied for DoA using the BIS index as the measured variable, namely, proportional-integral-derivative controllers (PID) [2], model predictive control (MPC) [3], adaptive control [4], neural [5] and fuzzy logic [6] control, in which case the results show the potential to reduce the amount of drug and to maintain hypnosis more accurately than the open-loop control performed with the current clinical practice.

The effect of the drug on the patient is highly dependent on the patient himself, leading to a high variability among patients, that brings high uncertainty to the automatic control design. This motivates the use of robust control design techniques to accomplish a controller with the appropriate performance to tackle these uncertainties. Robust control techniques applied to DoA have been reported in the bibliography, with predictive control [7] and with PID tuning control and CRONE control [8], a technique where a
A multiplicative description of non-parametric uncertainty is used in design. Internal model control (IMC) has been explored in [9], indicating better performances with patient uncertainties, compared with a PID controller. A robust deadbeat controller is designed in [10] that showed an improved performance in over/undershooting and settling time when compared with the performances of two PID based controllers.

The problem of control in the presence of model uncertainties and unmodeled dynamics is addressed in this report. The controller is computed based on $H_\infty$ theory control design and is designed to provide an adequate drug administration, with a good reference tracking and an output disturbance rejection, while stabilizing the class of possible patient models within the uncertainty bounds considered.

The report is organized as follows. After this brief introduction, the mathematical model is described in section 2 and the control synthesis is presented in section 3, where robust performance and robust stability are evaluated. Conclusions are drawn in section 4.

## 2 Pharmacokinetic/dynamic model for propofol

Models for propofol have been the subject of several publications [11–13]. This section describes the particular models used in a state-space form that is suitable to the purpose of this work. The effect of the hypnotic drug on the patient can be modeled by the interaction of three compartments, a central compartment where the drug is perfused, representing the main circulatory course of drug and its target, blood, liver and brain, that interacts with two peripheral compartments (figure 1). One compartment represents the

![Figure 1: Schematic representation of the multi-compartmental model for the dynamic response of hypnosis. The shadowed region is the PK part of the model.](image)

fast distribution of the drug from the central nervous system (CNS) to the
muscles and organs, and the other that represents the bones and fat tissue where the drug distribution is slow. These interactions form the pharmacokinetic model (PK) of the drug as it relates the drug dose administered to the patient \( u \) (ml/h) with the plasma concentration of the drug \( c_p \) (µg/ml).

The mathematical model that describes the drug-patient pharmacokinetics is written in state-space form as

\[
\begin{bmatrix}
\dot{m}_1 \\
\dot{m}_2 \\
\dot{m}_3
\end{bmatrix}
= \begin{bmatrix}
-k_{10} + k_{12} + k_{13} & k_{21} & k_{31} \\
k_{12} & -k_{21} & 0 \\
k_{13} & 0 & -k_{31}
\end{bmatrix}
\begin{bmatrix}
m_1 \\
m_2 \\
m_3
\end{bmatrix}
+ \begin{bmatrix}
10000 \\
0 \\
0
\end{bmatrix} u \tag{1}
\]

where \( m_i \) (µg), with \( i = 1, 2, 3 \), is the mass in the compartment \( i \), \( k_{ij} \) (s\(^{-1}\)), with \( i, j = 1, 2, 3 \), is the equilibrium constant from the \( i \)-th to the \( j \)-th compartment and \( V_1 \) (l) is the volume of the central compartment. Here, the drug concentration is considered to be 10 mg/ml.

The relation between the plasma concentration of the drug and its actual effect is referred to as the pharmacodynamic model (PD). The PD model encompasses the relation between the plasma concentration and the concentration in the effect compartment, and the relation between this last variable and the DoA level. The drug concentration in the effect compartment, \( c_e \), is described by

\[
\dot{c}_e = -k_{e0}c_e + k_{e0}c_p \tag{3}
\]

where \( k_{e0} \) (s\(^{-1}\)) is the equilibrium constant between the central and the effect-site compartments.

The drug effect observed on the patient may be expressed as a non-linear function of the effect-site concentration, such as

\[
BIS = E_0 + (E_{\text{max}} - E_0) \frac{c_e^\gamma}{c_e + C_{50}^\gamma} \tag{4}
\]

where \( E_0 \) is the baseline effect at zero concentrations, \( E_{\text{max}} \) is the peak drug effect, \( C_{50} \) is the concentration related with 50% of the drug effect and \( \gamma \) is the steepness of the concentration-response relation.

In anesthesia, two types of drugs affect the DoA level. The bigger effect is achieved by hypnotic drugs. In the case considered here, propofol is the hypnotic drug used. The other class of drugs that has an effect on DoA corresponds to the analgesic drugs. Again, here, remifentanil is the analgesic drug used. Hence, one has to distinguish between the variables associated with the hypnotic model, to which its added the super-index \( \text{prop} \), and the variables associated with the analgesic models, to which its added the super-index \( 3 \).
Therefore, $c_{\text{prop}}$ denotes the concentration in the effect compartment of propofol, and $c_{\text{remi}}$ denotes the concentration in the effect compartment of remifentanil. The existing correlation between the effect of analgesic drugs, such as remifentanil, and the effect of hypnotic drugs, in this case propofol, that have a synergic way, is expressed in the overall effect as

$$BIS = \frac{E_0}{1 + (U_{\text{prop}} + U_{\text{remi}})^\gamma},$$

(5)

where $U_{\text{prop}}$ and $U_{\text{remi}}$ are the normalized effect concentrations defined as

$$U_{\text{prop}} = \frac{c_{\text{prop}}}{C_{50}^{\text{prop}}}, \quad U_{\text{remi}} = \frac{c_{\text{remi}}}{C_{50}^{\text{remi}}}.$$

(6)

### 2.1 Model linearization

The linear part of the model (1–3) may be built in a state-space model such as

$$\begin{cases}
\dot{x}(t) = \Phi x(t) + \Gamma u(t) \\
p(t) = I x(t),
\end{cases}$$

(7)

where $\Phi$ is a patient dependent matrix defined as

$$\Phi = \begin{bmatrix}
-(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} & 0 \\
k_{12} & -k_{21} & 0 & 0 \\
k_{13} & 0 & -k_{31} & 0 \\
\frac{k_{eo}}{10000V_1} & 0 & 0 & -k_{eo}
\end{bmatrix},$$

(8)

$x$ is the state defined as

$$x = \begin{bmatrix}
m_1 \\
m_2 \\
m_3 \\
c_e
\end{bmatrix}, \quad \Gamma = \begin{bmatrix}
10000 \\
3600 \\
0 \\
0
\end{bmatrix}, \quad I = \begin{bmatrix}
0 & 0 & 0 & 1
\end{bmatrix},$$

(9)

and $t$ is the continuous time measured in seconds.

In the Laplace transform domain, the state-space system (7) is described by

$$c_e(s) = F(s)u(s),$$

(10)

where $F(s)$ is the transfer function of the linear part of the model and $s$ is the Laplace variable.

The linear approximation of the nonlinear description of the dependence of the observed effect (5) on the effect-site concentration is accomplished by the Jacobian linearization. From (5), at the equilibrium value of $BIS$, the equilibrium value of the effect-site concentration $c_e$ is

$$c_e = \left[ \frac{\sqrt{E_0}}{\sqrt{BIS}} - 1 - U_{\text{remi}} \right] C_{50}^{\text{prop}}.$$
The BIS derivative with respect to the increments of the effect-site concentration, $\eta$, is given by

$$
\eta = \frac{d}{dc_e} BIS \bigg|_{c_e = \bar{c_e}} = \frac{E_0 \gamma}{C_{50}^{prop}} \frac{\left( \frac{\bar{c_e}}{C_{50}^{prop}} + U_{remi} \right)^{\gamma-1}}{1 + \left( \frac{\bar{c_e}}{C_{50}^{prop}} + U_{remi} \right)^\gamma}^2,
$$

and represents the static gain of the nonlinear term of the model, that relates the increment of the drug effect-site concentration with its effect given by the increment of the BIS index with respect to its equilibrium value.

The nonlinear relation between the effect compartment concentration and the DoA level only affects the static gain of the linearized model, yielding two sources of uncertainties: change of the derivative with respect to the equilibrium point and parameters variability. The remifentanil dose appears in the model as a disturbance. Although one could take advantage of knowing its value, in this work this feedforward term is not considered.

From (12) and (10) the linearized model is described by

$$
BIS(s) = G(s) u(s),
$$

where $G(s)$, with $G(s) = F(s) \eta$, is the transfer function that relates the patient response, measured by the BIS index, with the drug dose.

### 3 Controller design for DoA

Clinically, the level of the depth of anesthesia at which the patient should be kept at is 50. In a feedback framework, as shown in figure 2, the controller is designed to compare the value of the BIS index with the desired level, and compute the amount of drug required to deliver to the patient. The drug is administered to the patient through a syringe connected to the computer, that samples the BIS index value every 5 seconds.

![Figure 2: Schematic representation of the control system](image-url)
In figure 2, the manipulated variable $u$ is the increment of the drug infusion flow with respect to the equilibrium, $y$ is the DoA level with respect to the equilibrium, $d$ is the sum of disturbances acting on the system, $r$ is the reference value for $y$, $n$ is the sensor noise signal and $K$ is the controller.

In the work described here, the $H_\infty$ optimal control design technique is used to design a suitable controller for this problem. The $H_\infty$ method approaches the control problem as an optimization problem in the frequency domain, in order to yield the desired time domain response. The main goal is to obtain a controller that is able to yield robust performance as well as robust stability, in the presence of model uncertainty. Load disturbances and sensor noise are also taken into account in the control design.

As depicted in figure 2, the control structure to design comprises the designed controller $K(s)$ that compares the reference, $r$, with the measured output, $y$, that is affected by sensor noise, $n$, and load disturbances, $d$. The closed-loop system is

$$y = \frac{1}{1+GK} d + \frac{GK}{1+GK} r - \frac{GK}{1+GK} n.$$  

(14)

The transfer function from $d$ to $y$ is the sensitivity function, $S(s)$, and the transfer function from $r$ to $y$ is the complementary sensitivity function, $T(s)$. The transfer function $n \rightarrow y$ is $-T(s)$.

### 3.1 Robust stability

The robust stability objective consists in synthesizing a stabilizing controller for all the plant models in a given class, $\mathcal{G} = \{G_i, i = 1, 2, ..., 20\}$. Appendix B provides the parameters for a set of models. This set of models is referred hereafter as the patient bank. For this sake, it is assumed that the true model $G(s)$ of a given patient can be written as a function of a nominal model $G_N(s)$ as

$$G(j\omega) = G_N(j\omega)(1 + \Delta(j\omega)).$$  

(15)

where $\Delta$ is the multiplicative uncertain dynamics at frequency $\omega$.

In figure 3, the frequency response of the models $G_i$ shows that there is a wide range of dynamic behaviors within these models. This can also be seen in figure 4, where the uncertainty $\Delta$ in (15) is shown for each model. This high variability in the dynamic behaviors makes it difficult to design a suitable controller for all the models. So, for the sake of obtaining a better controller in terms of performance, two models are not used for the controller design (models $G_4$ and $G_{14}$), being treated separately.

For robust stability analysis, the Nyquist stability criterion is called upon. Based on this criterion, the controller $K$ designed to stabilize the nominal model $G_N$, also stabilizes $G$ if

$$|KG_N(j\omega) - KG(j\omega)| < |1 + KG_N(j\omega)|.$$  

(16)
Figure 3: Frequency response of all the $G(s)$ models in the patient bank. The nominal model is represented in red.

Figure 4: Magnitude of the uncertainty $\Delta$ for the models $G_i$, $i = 1, \ldots, 20$, with respect to the nominal model $G_{15}$. The cover function (majorant) $W$ of all uncertainties, except of the models $G_4$ and $G_{14}$ (dashed black lines) that are excluded from this analysis, is represented in red.
This is called the robust stability condition and can be interpreted in geometrical terms in figure 5.

Figure 5: Schematic representation of the robust stability condition.

With (15), condition (16) can be written in the form

\[ |\Delta(j\omega)| < \frac{|1 + KG_N(j\omega)|}{|KG_N(j\omega)|}. \]  \hspace{1cm} (17)

Let \( l(\omega) \) be an upper bound function of the multiplicative uncertainty, meaning that

\[ |\Delta(j\omega)| = \frac{|KG_N(j\omega) - KG(j\omega)|}{|KG_N(j\omega)|} < l(\omega). \]  \hspace{1cm} (18)

Therefore, if \( l(\omega) \) is such that

\[ l(\omega) < \frac{|1 + KG_N(j\omega)|}{|KG_N(j\omega)|}, \]  \hspace{1cm} (19)

condition (16) is satisfied, and all the models that verify (19) will be stabilized by the controller \( K \).

Condition (19) may be written in the form

\[ \frac{1}{l(\omega)} > \frac{|KG_N(j\omega)|}{|1 + KG_N(j\omega)|} = |T_N(j\omega)|, \]  \hspace{1cm} (20)

where \( T_N \) is the complementary sensitivity function obtained with the nominal model and corresponds to the closed-loop transfer function obtained when the controller is coupled with the nominal model. Thus, if an upper bound function \( l(\omega) \) for the multiplicative uncertainties exists such that \( l^{-1}(\omega) \) is also an upper bound for the complementary sensitivity function, the controller designed for the nominal model has robust stability, meaning that all the systems \( G_i \) that satisfy (19) are stabilized by the nominal controller.
3.2 Robust performance

In terms of performance, the controller is expected to be robust as it is
designed to reject load disturbances and high frequency sensor noise, in the
presence of model uncertainty.

The load disturbance rejection objective is defined as a weighted sensitivity
minimization problem and the measurement noise rejection objective is de-
fined as a weighted complementary sensitivity minimization problem. These
two goals are closely related through the specification of the controlled system
bandwidth (by the sensitivity function) and reference tracking and robust
stability specifications (related to the complementary sensitivity function).

In order to tackle the above minimization problems, two weighting functions
are incorporated in the system, as depicted in figure 6. In this case, $W_S$

![Figure 6: Schematic representation of the control action with the weighting functions.](image)

and $W_T$ affect the sensitivity and the complementary sensitivity functions,
respectively, and the closed-loop system is

$$y = \frac{1}{1 + GK} W_S d + \frac{GK}{1 + GK} r - \frac{GK}{1 + GK} W_T n,$$

(21)

Since, for performance purposes of rejecting load disturbances, the gain of
the weighted sensitivity function must be kept below 1, then it must be

$$|S \times W_S| < 1 \iff |S| < \frac{1}{|W_S|},$$

(22)

where $S$ is the sensitivity function given by

$$S = \frac{1}{1 + GK}.$$  

(23)

This weighted sensitivity function enforces the desired bandwidth while the
weighted complementary sensitivity function enforces the adequate roll-off
outside the bandwidth in which the disturbances are rejected.
The noise rejection problem is approached in the same way, as the gain of the weighted complementary sensitivity function must be kept below 1, so that

\[ |T \times W_T| < 1 \iff |T| < \frac{1}{|W_T|}. \]  

(24)

where \( T \) is the complementary sensitivity function given by

\[ T = \frac{GK}{1 + GK}. \]  

(25)

Conditions (22) and (24) must be satisfied for each \( S_i \) and \( T_i \), with \( i = 1, \ldots, 20 \) of all \( G_i \) models. This is achieved by selecting \( W_S \) and \( W_T \) to have the frequency response shown in figure 7.

The weight \( W_T^{-1} \) is a low-pass function whose shape is selected such as to ensure reference tracking up to the desired bandwidth (that implies that \( W_T^{-1} \) is small) and noise rejection in the higher frequency band, as well as robustness with respect to high frequency model uncertainty (that implies that \( W_T^{-1} \) is big in this band). A dual behavior follows to \( W_S^{-1} \).

The controller is also designed with integral action in order to overcome possible steady-state errors, as depicted in figure 8, where \( I \) is the integral term and \( K = CI \).
3.3 Controller performance and stability analysis

With all the performance and robust stability issues taken into account, the controller synthesis is performed using the DK algorithm for \( \mu \)-synthesis [14] in the implementation provided by the function \texttt{dksyn} of MATLAB\textsuperscript{®}, described by \textit{Robust Control Toolbox} \textsuperscript{TM} User’s Guide [15], as explained in Appendix A. The controller is a state-space model and is designed for the nominal model \( G_{15} \) with the \( W_S \) and \( W_T \) of figure 7, being expressed as

\[
\begin{align*}
\dot{x}_c(t) &= A \, x_c(t) + B \, e(t) \\
u(t) &= C \, x_c(t),
\end{align*}
\]

where \( A, B \) and \( C \) are the matrices that result from the design algorithm, \( e \) is the tracking error as, \( e = r - y_m \), and \( x_c \) is the controller state.

The loop gain frequency response and the Nyquist plot are presented in figures 9 and 10, respectively. These plots show that the systems are stable with the controller designed, since the stability condition

\[
|KG(j\omega)| < 1 \quad \text{at} \quad \angle KG(j\omega) = -180^\circ
\]

is fulfilled and the Nyquist curves of all the models are drawn on the same side with respect to the point \( s = -1 \), as the one corresponding to the nominal model.

The robust stability condition, that relies on the existence of an upper bound function \( l(\omega) \) that yields conditions (19) and (20), is fulfilled as shown in figures 11 and 12. The frequency responses of \( l(\omega) \), in figure 11, and of \( l^{-1}(\omega) \), in figure 12, show that this controller is robustly stable except for the models excluded from the design (\( G_4 \) and \( G_{14} \)).

The performance condition expressed in (22) is represented in figure 13, showing that there is one model (\( G_2 \)) for which the condition is not satisfied.
Figure 9: Frequency response of the loop gain controlled systems. The nominal model is represented in red.

Figure 10: Nyquist plot of the controlled systems. The nominal model is represented in red.
Figure 11: Magnitude of the multiplicative uncertainty $\Delta$ of the loop gain of the controlled systems. The function $l(\omega)$ is represented in red. The dashed black lines represent the uncertainty of models $G_4$ and $G_{14}$ (that are excluded from this analysis).

Figure 12: Gain of the inverse upper bound function for multiplicative uncertainty $l^{-1}(\omega)$ and the nominal complementary sensitivity function $T_N$. This plot is used to verify the robust stability condition.
On the other hand, the noise rejection condition (24) is met since all models fall below the inverse of function $W_T$ (fig. 14).

The controller designed is able to track a constant reference for the different models but presents an apparent static error for some models (fig. 15) that disappears with time scaling (fig. 16), as ensured by the integral action.

In spite of the controller not being able to a priori guarantee stability for models $G_4$ and $G_{14}$, the time response of the controller with model $G_4$ (fig. 15) shows that the controller is able to provide an acceptable performance. The range of behaviors within these models is depicted in the step response in figure 15, being in accordance with the frequency response of the loop gain of the controlled systems (fig. 9).

The simulations are performed in the presence of noise, produced by a white-noise signal, with power 5, filtered by a function which frequency response is plotted in figure 17. The resultant sampled noise is plotted in figure 18, and when compared with the normalized noise of real data shows similar frequency and gain.
Figure 14: Gain of the complementary sensitivity functions $T$ and of the upper bound $W^{-1}$. This plot is used to check the robust performance condition in what concerns reference tracking.

Figure 15: Time response of the controlled systems and the control action ($u$) for 5 models ($G_1$, $G_2$, $G_4$, $G_8$ and $G_N$). The reference is represented by the red dashed line.
Figure 16: Time response of the nominal controlled system. The reference is represented by the red dashed line.

Figure 17: Frequency response of the band-limiting filter for noise simulation.
Figure 18: Simulated noise and noise of real data from two different patients.
3.4 Order reduction

For computer application, the 21st–order controller that directly results from the \(\mu\)-synthesis design procedures is approximated by a lower order of 5 (appendix A). The order reduction is performed without the integral term for which the controller of order 20 is reduced to a 4th–order. The Hankel singular value plot of the controller state-space representation, depicted in figure 19, shows that the majority of the system characteristics is well preserved in the 4th–order controller.

![Hankel singular value plot for the controller order reduction.](image)

After the controller is augmented with the integrator, the loop gain frequency response of the nominal model is compared with the full order controller, in figure 20, as well as the Nyquist curves figure 21, showing that this order reduction is adequate. The sensitivity and complementary sensitivity functions of the reduced-order controller are also compared in figure 22 with the ones of the full order controller. Figure 23 shows a simulation of the time response. This comparison shows a very good agreement between both controllers in the frequency range of interest, that justifies the use of the reduced complexity one. The use of a higher order, in this reduction, does not bring significant changes in frequency and time responses, in contrast with the use of orders lower than 4, that greatly affects frequency and time responses.
Figure 20: Frequency response of the loop gain controlled nominal model with the full order controller and with the reduced-order controller ($L^R_N$).

Figure 21: Nyquist curves of the controlled nominal model with the full order controller (blue) and with the reduced-order controller (red).
Figure 22: Gain of the sensitivity and complementary sensitivity functions of the controlled nominal model with the full order controller and the reduced-order controller ($S_R^N$, $T_R^N$).

Figure 23: Time response of the controlled nominal model with the full order controller and the reduced-order controller ($G_R^N$). The reference is represented by the red dashed line.
3.5 Controller discretization

The controller designed in continuous time is discretized with the zero-order hold method, with a sampling time of 5 seconds. The loop gain of the systems with the reduced and discrete controller is presented in figure 24, and allows to conclude that the stability condition is met for all controlled systems. The Nyquist curves of figures 25 corroborates the previous statement.

The robust stability condition for the discrete controller is fulfilled as concluded from figures 26 and 27, since the inverse of the upper bound function for all uncertainties (except for models $G_4$ and $G_{14}$) is the upper bound of the complementary sensitivity function.

The robust stability of this controller is accomplished at the expense of performance as shown in figures 28 and 29, where it is observed that the performance conditions for load disturbance rejection and noise rejection are not fulfilled for all the models.

The controlled time response of a few models ($G_1$, $G_2$, $G_4$, $G_8$ and $G_N$) of the database is presented in figure 30. For model $G_1$, the controller stabilizes the system and yields the performance conditions (22) and (24). Model $G_4$ is one of the two models excluded from the controller design, but the controller presents a good performance when applied to it. Although the controller does not yield condition (22) for model $G_8$ and condition (24) for model $G_N$, it is able to stabilize those systems and provide acceptable performances in time response.

![Frequency response of the loop gain systems, with the discrete controller. The nominal model is represented in red.](image)

Figure 24: Frequency response of the loop gain systems, with the discrete controller. The nominal model is represented in red.
Figure 25: Nyquist plot of the loop gain systems, with the discrete controller. The nominal model is represented in red.

Figure 26: Magnitude of the multiplicative uncertainty of the loop gain systems, with the discrete controller. Represented in red is the $l(\omega)$ function. The dashed black lines represent the uncertainty of models $G_4$ and $G_{14}$ (that are excluded from this analysis).
Figure 27: Gain of the inverse upper bound function for multiplicative uncertainty $l^{-1}(\omega)$ and the nominal complementary sensitivity function $T_{N,d}^R$, with the discrete controller.

Figure 28: Gain of the sensitivity functions $S_{N,d}^R$ and upper bound $W_{S,d}^{-1}$, with the discrete controller.
Figure 29: Gain of the complementary sensitivity functions $T_{R,N,d}^R$ and upper bound $W_{T,d}^{-1}$, with the discrete controller.

Figure 30: Time response of the controlled systems, with the discrete controller, and the control action for 5 models ($G_1$, $G_2$, $G_4$, $G_8$ and $G_N$). The reference is represented by the red dashed line.
4 Conclusions

The controller that is designed aiming at robust performance and stability is able to tack the reference for all models. This controller has robust stability for 18 of the 20 models, although the time responses for the two other models left out are considered appropriate. The performance condition is not satisfied for all models as the sensitivity function of one model does not fall below the bound $W_{S^{-1}}$.

With discretization, a few discrete complementary sensitivity functions do not fall below the discrete $W_{T^{-1}}$ bound. Nevertheless, the robust stability condition is fulfilled. The order reduction and the a posteriori discretization do not bring any significant changes to frequency and time responses. The fact that the bounds of performance are crossed is the cost for robust stability, that is the ultimate goal to achieve at the problem at hand.

An approach to the robust control of DoA based on $H\infty$ design and $\mu$-synthesis has been proposed and illustrated using a bank of patient data. The approach consists in characterizing a multiplicative uncertainty model description for the patients, enlarging this model with an integrator to ensure zero steady-state tracking error, controller design using the DK-algorithm, controller order reduction, and controller redesign in discrete time to obtain a controller suitable to computer application.
References


Appendix A – Controller Algorithm

A.1 Controller synthesis

The controller design is performed using the dksyn function of the Robust Control Toolbox™ for MATLAB®. This function returns the controller, as a state-space model, and the robust performance indicator $\gamma_p$ (\texttt{bnd}) of the closed-loop uncertain system.

The system for which the controller is designed is represented by the shaded region in figure 31. Since it is impossible to impose integral action directly on the controller, the systems $G(s)$ are augmented with an integrator and, for this sake, are referred as $GI$.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{control_system}
\caption{Schematic representation of the control action with the weighting functions.}
\end{figure}

To model the uncertainty a few operations are performed. First, the set of 20 models are defined as transfer functions, $GI(s)$, and grouped in a LTI array with the function \texttt{stack}:

\begin{verbatim}
GI_array = stack(1,GI_1, ...,GI_20);
\end{verbatim}

Afterwards, the \texttt{ucover} function is applied using the resultant array and the nominal model $GI_N(s)$.

\begin{verbatim}
[GI,Info] = ucover(GI_array,GI_N,ord,'InputMult');
\end{verbatim}

This results in an uncertain model that covers all the behaviors of the array and is in the form $GI = GI_N(1 + W(s)\Delta(s))$. Here, $\Delta$ is the uncertain dynamics, and is defined as multiplicative uncertainty on the \texttt{cover} function input \texttt{'InputMult'}. The filter $W$ is given by \texttt{Info.W1}, with user-defined order \texttt{ord} (in this case is of order 3), is a stable minimum-phase shaping
filter that adjusts the amount of uncertainty at each frequency and is also an output of this function and is implicitly used to compute the controller. The interconnections of the system are defined by the function `sysic`. First, the systems used for the design are put together as well as its inputs, in the form

```matlab
systemnames = 'GI WS WT';
inputvar = '[d;n;uI]';
```

Then, the inputs must be grouped with the systems, as

```matlab
input_to_GI = '[uI]';
input_to_WS = '[d]';
input_to_WT = '[n]';
```

and the output variables are defined as an algebraic result of the open-loop system

```matlab
outputvar = '[GI+WS; -GI-WS-WT]';
```

where the first output corresponds to the actual output \( y = GI \times u_I + WS \times d \), and the second corresponds to the measurable output that enters the controller, \( y_m = -GI \times u_I - WS \times d - WT \times n \). Finally the system is defined as \( P \),

```matlab
P = sysic;
```

The controller is then computed with the function `dksyn`, which inputs are the uncertain state-space model, with defined inputs and outputs, and the number of measurement and control channels, that are, in this case, one measurement channel \( (y_m) \) and one control channel \( (u_I) \). The `dksyn` function is then applied to the uncertain plant model \( P \),

```matlab
[C,~,bnd] = dksyn(P,1,1);
```

resulting in the controller \( C \), of order 20, that is put in series with the integrator \( I \), and is referred as \( K \).

If the robust performance indicator \( \gamma_p(\text{bnd}) \) is near 1, the performance objectives have been achieved and the desired and effective closed-loop bandwidths match closely. If this value is less than 0.85 the achievable performance can be improved upon and if is greater than 1.2, the desired closed-loop bandwidth is not achievable for the given amount of plant uncertainty. In this case, \( \gamma_p \) is 1.1567 being inside the range of the achievable performance.
A.2 Order reduction

The controller designed is a 20th-order controller that can be simplified to a specific order with the function `reduce`. In this case, the controller is reduced to order four as

\[
Cr = \text{reduce}(C, 4, 'Display', 'on');
\]

and a Hankel singular value plot is displayed in figure 19. The reduce controller \( CR \) is augmented with the integrator.

A.3 Discretization

The reduced-order controller \( CR \) is discretized, with zero-order hold method and a sampling time of 5 seconds, using the function `c2d`:

\[
Cd = \text{c2d}(Cr, 5);
\]

The resulting controller is augmented with the integrator in discrete time, and is described in the state-space form, as defined in (26), and its matrices are, thus,

\[
A = \begin{bmatrix}
0.5310 & 0.6723 & 0.0960 & -0.1526 & 0.3123 \\
-0.6716 & 0.1383 & 0.1787 & -0.0751 & 0.4618 \\
-0.0968 & 0.1788 & 0.6808 & 0.2836 & -0.1028 \\
-0.1525 & 0.0743 & -0.2861 & -0.1065 & -0.0490 \\
0 & 0 & 0 & 0 & 1.0000
\end{bmatrix}, \quad (28)
\]

\[
B = \begin{bmatrix}
0 \\
0 \\
0 \\
0 \\
5
\end{bmatrix}, \quad (29)
\]

\[
C = \begin{bmatrix}
0.0008 & -0.1262 & 0.0008 & -0.1220 & 0
\end{bmatrix}. \quad (30)
\]
## Appendix B – Model Data

**Table I: Parameter values for the model bank $\mathcal{G} = \{G_i, i = 1, 2, \ldots, 20\}$.**

<table>
<thead>
<tr>
<th>$e_1$ ($l^{-1}$)</th>
<th>$k_{10}$ ($s^{-1}$)</th>
<th>$k_{12}$ ($s^{-1}$)</th>
<th>$k_{21}$ ($s^{-1}$)</th>
<th>$k_{30}$ ($s^{-1}$)</th>
<th>$c_{\text{prop}}^{\text{lip}}$ $\mu g/ml^{-1}$</th>
<th>$c_{\text{remi}}^{\text{lip}}$ $\mu g/ml^{-1}$</th>
<th>$\gamma$</th>
<th>$E_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$G_1$</td>
<td>0.27</td>
<td>1.60e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>3.08e-03</td>
<td>50</td>
</tr>
<tr>
<td>$G_2$</td>
<td>0.32</td>
<td>4.67e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>1.83e-03</td>
<td>50</td>
</tr>
<tr>
<td>$G_3$</td>
<td>0.11</td>
<td>1.11e-02</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>3.48e-03</td>
<td>50</td>
</tr>
<tr>
<td>$G_4$</td>
<td>0.19</td>
<td>3.59e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>9.79e-03</td>
<td>50</td>
</tr>
<tr>
<td>$G_5$</td>
<td>0.40</td>
<td>1.50e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>2.75e-02</td>
<td>50</td>
</tr>
<tr>
<td>$G_6$</td>
<td>0.29</td>
<td>1.08e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>3.80e-02</td>
<td>50</td>
</tr>
<tr>
<td>$G_7$</td>
<td>0.20</td>
<td>2.81e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>7.43e-03</td>
<td>50</td>
</tr>
<tr>
<td>$G_8$</td>
<td>0.14</td>
<td>1.53e-02</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>3.56e-03</td>
<td>50</td>
</tr>
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<td>$G_9$</td>
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<td>1.11e-02</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>3.37e-03</td>
<td>50</td>
</tr>
<tr>
<td>$G_{10}$</td>
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<td>1.48e-02</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>1.53e-03</td>
<td>50</td>
</tr>
<tr>
<td>$G_{11}$</td>
<td>0.16</td>
<td>5.47e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>5.02e-03</td>
<td>50</td>
</tr>
<tr>
<td>$G_{12}$</td>
<td>0.26</td>
<td>1.44e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>1.87e-03</td>
<td>50</td>
</tr>
<tr>
<td>$G_{13}$</td>
<td>0.28</td>
<td>1.01e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>2.49e-02</td>
<td>50</td>
</tr>
<tr>
<td>$G_{14}$</td>
<td>0.28</td>
<td>8.09e-04</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>2.86e-03</td>
<td>50</td>
</tr>
<tr>
<td>$G_{15}$</td>
<td>0.23</td>
<td>1.08e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>2.23e-02</td>
<td>50</td>
</tr>
<tr>
<td>$G_{16}$</td>
<td>0.34</td>
<td>3.56e-04</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>9.30e-03</td>
<td>50</td>
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<tr>
<td>$G_{17}$</td>
<td>0.32</td>
<td>2.31e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>2.80e-03</td>
<td>50</td>
</tr>
<tr>
<td>$G_{18}$</td>
<td>0.21</td>
<td>7.21e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>4.37e-03</td>
<td>50</td>
</tr>
<tr>
<td>$G_{19}$</td>
<td>0.33</td>
<td>8.85e-04</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>2.20e-02</td>
<td>50</td>
</tr>
<tr>
<td>$G_{20}$</td>
<td>0.29</td>
<td>2.47e-03</td>
<td>1.87e-03</td>
<td>6.98e-04</td>
<td>9.17e-04</td>
<td>5.5e-05</td>
<td>4.82e-03</td>
<td>50</td>
</tr>
</tbody>
</table>

IV
Appendix C – MATLAB® Code

The MATLAB® code for controller synthesis is presented in this appendix. Note that all variables are referred on the main body of the report and on the appendix A, with the exception of model matrices $A_m$, $B_m$ and $C_m$ that refers to the matrices $\Phi$, $\Gamma$ and $I$, respectively, of system (7).

Note that variables $\text{gamm}$, $\text{bet}$ and $\text{eta}$ are, the variables $\gamma$, $\beta$ and $\eta$, respectively.

To be highlighted is the fact the time unit in control design algorithm is seconds, and the results are properly shown with time in minutes.

The string space is represented by the character $\_\_\_\_\_\_\_\_\_\_

The MATLAB® Code is:

clear all

% Load 20 model data : variable => data
load('data_doa.mat') % 20x12 matrix

%% Transfer functions for the 20 models
for n=1:20

% PK/PD model parameters
v1 = data(n,1); k10 = data(n,2);
k12 = data(n,3); k13 = data(n,4);
k21 = data(n,5); k31 = data(n,6);
ke0 = data(n,7); C50_remi = data(n,8);
C50_prop = data(n,9); gamm = data(n,10);
bet = data(n,11); E0 = data(n,12);

% Normalized effect concentration of remifentanil,
% considered null
U_remi = 0;

% Model Linearization at the equilibrium value
% of BIS = 50%
ref=50; % y => BIS => DoA level

% effect concentraion at equillibrium value
ce_ref = C50_prop * ((E0/ref-1)^(1/gamm)-U_remi);

% Nonlinear static gain
eta = -E0/C50_prop * gamm * (ce_ref/C50_prop +...
    U_remi)^(gamm-1)/( (1+(ce_ref/C50_prop +...
    U_remi)^gamm)^(gamm) );

% Drug dose reference for BIS = 50%
u_ref = k10 * 3600/10000 * 1000*v1 * ce_ref;

v
\[
A_m = \begin{bmatrix}
-k_{10} & -k_{12} & -k_{13} & k_{21} & k_{31} & 0 \\
-k_{12} & -k_{21} & 0 & 0 & 0 & 0 \\
k_{13} & 0 & -k_{31} & 0 & 0 & 0 \\
\frac{ke_0}{1000*v_1} & 0 & 0 & 0 & -ke_0 & 0
\end{bmatrix}; \\
B_m = \begin{bmatrix}
10000/3600 \\
0 \\
0 \\
0
\end{bmatrix}; \\
C_m = \begin{bmatrix}
0 & 0 & 0 & 1
\end{bmatrix};
\]

State-space model matrices:
\[
x' = A_m x + B_m u, \quad ce = C_m x
\]

State-space model of the linear part of the model:
\[
F = \text{ss}(A_m, B_m, C_m, 0); \quad \%	ext{(Continuous state-space model)}
\]

State-space model to transfer function:
\[
[num, den] = \text{tfdata}(F); \quad \%	ext{(cell)}
\]

Numerator of the linearized model transfer function G:
\[
G_{\text{num}} = \eta * \text{num}(1,1); \quad \%	ext{(vector)}
\]

Denominator of the model transfer function G,
\[
G_{\text{den}} = \text{den}(1,1); \quad \%	ext{(vector)}
\]

Cell with all models:
\[
G{1,n} = \text{tf}(G_{\text{num}}, G_{\text{den}}); \quad \%	ext{(cell)}
\]

Cell with all models augmented with the integrator:
\[
G{I1,n} = \text{tf}(G_{\text{num}}, [G_{\text{den}} 0]); \quad \%	ext{(cell)}
\]

All models augmented with the integrator grouped in a LTI array:
\[
G_{\text{I-array}} = \text{stack}(1, G{1,1}, G{1,2}, G{1,3}, G{1,4}, \ldots
G{1,5}, G{1,6}, G{1,7}, G{1,8}, G{1,9}, G{1,10}, \ldots
G{1,11}, G{1,12}, G{1,13}, G{1,14}, G{1,15}, \ldots
G{1,16}, G{1,17}, G{1,18}, G{1,19}, G{1,20});
\]

Transfer function of the Nominal model:
\[
G_{\text{I-N}} = G{I1,15}; \quad \%	ext{(Continuous transfer function)}
\]

Uncertain model:
\[
\%	ext{Exclusion of models 4 and 14 from the analysis}
\%	ext{models = [1:3 5:13 15:20]; \%	ext{(vector)}
\%	ext{Order of filter W}
\%	ext{order = 3;}
\%	ext{Creation of the uncertain model GI}
\%	ext{[GI, Info] = ucover(GI_array(:,:,models,1), G_{I-N}, order,...
\%	ext{'InputMult'); \%	ext{(Continuous state-space system with
\%	ext{8 States, 1 Output, 1 Input)
\%	ext{Filter W}:
\%	ext{W = Info.W1; \%	ext{(Continuous state-space system with
\%	ext{VI}}
}
% 3 States, 1 Output, 1 Input)

%% Weighting functions WS and WT
WS = makeweight(db2mag(25),0.003,db2mag(-10));
WT = makeweight(db2mag(-10),0.4,db2mag(30));
% (Continuous state-space systems with 1 State, 1 Output,
% 1 Input)

%% System interconnection with inputs and outputs
systemnames = 'GI WS WT'; % (string)
inputvar = '[d;n;uI]'; % (string)
input_to_GI = '[uI]'; % (string)
input_to_WS = '[d]'; % (string)
input_to_WT = '[n]'; % (string)
outputvar = '[GI+WS; -GI-WS-WT]'; % (string)
P = sysic; % (Continuous uncertain state-space system
% with 10 States, 2 Outputs, 3 Inputs)

%% Controller Computation:
[C,~,bnd] = dksyn(P,1,1); % (C : Continuous state-space
% system with 20 States, 1 Output, 1 Input)

%% Order Reduction
Cr = reduce(C,4,'Display','on'); % (Continuous state-space
% system with 4 States, 1 Output, 1 Input)

%% Controller Discretization
h=5; % Sampling time
Cd = c2d(Cr,h); % (Discrete state-space system with
% 4 States, 1 Output, 1 Input)

%% Controller augmented with the integrator
% Integrator
Id = ss(1,h,1,0,h); % (Discrete state-space system)
K = Cd * Id; % (Discrete state-space system
% with 5 States, 1 Output, 1 Input).