Depth of Anesthesia:
A Study on Robust Control Design with Model Clustering

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Abstract

This report presents a case study on the design of a robust pole-placement controller for the level of hypnosis (DoA) for patients subject to general anesthesia, induced by the drug propofol. The model that describes the the level of hypnosis as a function of the drug dose is described and a pole-placement controller is designed. This controller is designed with polynomial techniques and is designed to be robustly stable for the class of models considered. The controller is evaluated for performance and robust stability.

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.

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 obtain a controller with the appropriate performance to tackle these uncertainties.

The report is organized as follows. After this brief introduction on the subject, the pharmacokinetic and pharmacodynamic model for DoA is presented in section 2. Controller design is presented in section 3, as well as its evaluation. Conclusions are drawn in section 4.

2 Pharmacokinetic/Pharmacodynamic model

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 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

\[
\begin{bmatrix}
\dot{m}_1 \\
\dot{m}_2 \\
\dot{m}_3
\end{bmatrix} =
\begin{bmatrix}
-k_{10} + k_{12} + k_{13} & k_{21} & k_{31} \\
k_{12} & -k_{21} & 0 \\
k_{13} & 0 & -k_{31}
\end{bmatrix}
\begin{bmatrix}
m_1 \\
m_2 \\
m_3
\end{bmatrix} +
\begin{bmatrix}
10000 \\
3600 \\
0
\end{bmatrix} u \tag{1}
\]

\[
c_p = \left[ \frac{1}{1000 \times V_1} \right] \begin{bmatrix}
m_1 \\
m_2 \\
m_3
\end{bmatrix}, \tag{2}
\]

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

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

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

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

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

(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.

### 2.1 Interaction with analgesic drugs

Bouillon et al. showed in [2] that the synergetic effect of the analgesic drug remifentanil on propofol administration is present in the electroencephalographic measure BIS. Therefore, an interaction model should be used for the DoA response. The DoA response as a function of the effect-site concentration for propofol and remifentanil interaction is

\[ BIS \,(\%) = E_0 \left( 1 - \frac{\left( \frac{U^{\text{prop}} + U^{\text{remi}}}{U_{50}} \right)^\gamma}{1 + \left( \frac{U^{\text{prop}} + U^{\text{remi}}}{U_{50}} \right)^\gamma} \right), \]  

(5)

where \( U^{\text{prop}} \) and \( U^{\text{remi}} \) are the normalized effect concentrations of propofol and remifentanil, respectively, and defined as

\[ U^{\text{prop}} = \frac{c_e^{\text{prop}}}{C_{50}^{\text{prop}}}, \quad U^{\text{remi}} = \frac{c_e^{\text{remi}}}{C_{50}^{\text{remi}}}, \]  

(6)

where \( C_{50}^{\text{prop}} \) and \( C_{50}^{\text{remi}} \) are the concentrations related with 50 % of the effect of propofol and remifentanil, respectively, and

\[ U_{50} = 1 - \beta \theta + \beta \theta^2, \]  

(7)

with

\[ \theta = \frac{U^{\text{prop}}}{U^{\text{prop}} + U^{\text{remi}}}. \]  

(8)

The PD model may be written in the reduced form

\[ BIS \,(\%) = E_0 \frac{1}{1 + \left( \frac{U^{\text{prop}} + U^{\text{remi}}}{1 - \beta U^{\text{prop}} U^{\text{remi}} (U^{\text{prop}} + U^{\text{remi}})^2} \right)^\gamma}, \]  

(9)

that, from the available models \( \beta = 0 \), and the model is reduced to

\[ BIS \,(\%) = \frac{E_0}{1 + \left( U^{\text{prop}} + U^{\text{remi}} \right)^\gamma}. \]  

(10)
2.2 Linear model for DoA

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

\[
\begin{align*}
\dot{x}(t) &= \Phi x(t) + \Gamma u(t) \\
c_e(t) &= I x(t),
\end{align*}
\]

(11)

where \(\Phi\) is a patient dependent matrix defined as

\[
\begin{bmatrix}
-(k_{10} + k_{12} + k_{13}) & k_{21} & k_{31} & 0 \\
k_{12} & -k_{21} & 0 & 0 \\
k_{13} & 0 & -k_{31} & 0 \\
k_{eo} & 0 & 0 & -k_{eo}
\end{bmatrix}
\]

(12)

\(x\) is the state defined as

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

(13)

and \(t\) is the continuous time measured in seconds.

In the Laplace transform domain, the state-space system (11) is described by

\[
c_e(s) = F(s)u(s),
\]

(14)

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 (10) on the effect-site concentration is accomplished by the Jacobian linearization. From (10), at the equilibrium value of \(\text{BIS}\), the equilibrium value of the effect-site concentration \(c_e\) is

\[
c_e = \left[\gamma \sqrt{E_0} \text{BIS} - 1 - U_{\text{remi}}\right] C_{50}^{\text{prop}}.
\]

(15)

The BIS derivative with respect to the increments of the effect-site concentration, \(\eta\), is given by

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

(16)

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.

From (16) and (14) 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 \( (y) \) with the desired level \( (r) \), and compute the amount of drug \( (u) \) 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. The linearized DoA model \( G(s) \) is discretized with the zero-order hold method, described in [3], using a sampling interval of 10 seconds. In discrete time, the DoA model is defined by the discrete time transfer function

\[ G_D(z) = \frac{B(z)}{A(z)}, \]

where \( A(z) \) and \( B(z) \) are polynomials in the \( Z \)-transform variable \( z \). At instant \( k \), in input-output form, the model is

\[ A(q)y(k) = B(q)u(k), \]

where \( A(q) \) and \( B(q) \) are polynomials in the forward-shift operator \( q \). Model parameters are strongly dependent on the patient (inter-patient variability) and may even vary for the same patient over time. This high variability motivates the design of a robust controller, in order to be able to stabilize this wide range of behaviors.
The control action in the input-output form is described by

\[ R(q)u(k) = T(q)r(k) - S(q)y(k), \]  

(20)

where \( R(q) \), \( T(q) \) and \( S(q) \) are polynomials in the forward-shift operator \( q \), and is depicted in figure 3.

Figure 3: Block diagram of the polynomial controller for the NMB response. The variables \( \bar{r}, \bar{u} \) and \( \bar{y} \) are, respectively, the values of the reference, the manipulated variable and the DoA level that correspond to the equilibrium considered.

The robust pole-placement controller is designed with polynomial techniques, as described in [4], and the results with the PKPD model for propofol behavior in the depth of anesthesia model (1 – 3, 10) is presented in this section.

### 3.1 Clustering

From a database of 20 models \( \mathcal{M} = \{ M_i, i = 1, 2, ..., 20 \} \), defined in appendix, 3 clusters are formed and a centroid model is defined for each cluster. This clustering procedure is carried out using the Vinnicombe metric \( \delta_\nu \). The clusters are defined by imposing \( \delta_\nu < 0.3 \) between all models in the same cluster. For each cluster the centroid is the model that minimizes the sum of all \( \delta_\nu \) distances between the centroid and the remaining models in the cluster.

### 3.2 Performance and robustness

Time response to a bolus infusion is presented in figure 4, for all the models, where the high variability of behaviors is apparent. The frequency responses are presented in figures 5-8, where the similarities between models in the same cluster, particularly at the high frequencies, are shown. Overall, models from cluster \( C_1 \) exhibit a higher gain than models of cluster \( C_2 \) and models of cluster \( C_3 \) present the lower gains.

The controller is designed for the nominal model (centroid model), with high frequency noise rejection, without integral action and with 4 real poles. The
Figure 4: Time response of the BIS (y) induced by a *bolus* dose. Cluster $C_1$ are represented in blue, $C_2$ in pink and $C_3$ in green.

Figure 5: Frequency response of models of cluster $C_1$ (blue), $C_2$ (pink) and $C_3$ (green).
Figure 6: Frequency response of models of cluster C1, highlighting the centroid.

Figure 7: Frequency response of models of cluster C2, highlighting the centroid.
Figure 8: Frequency response of models of cluster $C_3$, highlighting the centroid.

zero on the left-plane is not cancelled and the observer polynomial has order two.

The desired closed-loop transfer function is defined by the following polynomials

$$B_m(z) = k(z - z_1)z^2$$
$$A_m(z) = (z - p)^4,$$

where $k$ is the static gain, $z_1$ is the referred zero and $p$ is the real pole. The choice of the real pole $p$ defines the closed-loop transfer function.

### 3.2.1 Cluster $C_1$

For the first cluster $C_1$, defined by models $M_i$, with $i = 3, 4, 6, 7, 11, 13, 14, 15, 19$ and with the centroid model $M_{13}$, the desired closed-loop transfer function, that results from the choice of $p = 0.97$, is defined by polynomials

$$A_m = z^4 - 2.4000 \ z^3 + 2.1600 \ z^2 - 0.8640 \ z + 0.1296$$
$$B_m = 1.3407 \times 10^{-2} \ z^3 + 1.2193 \times 10^{-2} \ z^2.$$
A value of $g = 0.6$ is used. The controller is defined by polynomials

\[ R_{C1} = z^4 - 2.6264 \, z^3 + 2.4475 \, z^2 - 1.0103 \, z + 0.1893 \]
\[ S_{C1} = -0.1130 \, z^4 + 0.1932 \, z^3 + 0.0312 \, z^2 - 0.1932 \, z + 0.0818 \]
\[ T_{C1} = -0.0488 \, z^4 + 0.0947 \, z^3 - 0.0459 \, z^2. \]

The action of the controller designed for cluster $C1$ is presented in figure 9.

![Figure 9](image-url)

Figure 9: Time response and control action simulations, with Simulink®, of the controller defined for cluster $C1$. The centroid model is represented in black.

Although all models present an acceptable response in the presence of high frequency noise, a model, $M_{14}$ shows an oscillatory mode that is explained by the resonance peaks at 0.02 rad/s in figures 10 and 12, where the frequency response of the closed-loop transfer functions from the reference to the output (BIS) and to the input (dose), respectively, are represented.

The open-loop controlled system frequency responses are presented in figure 11, where it is observed that the stability condition holds for all models. Since there are three models with positive multiplicative uncertainties (figure 13), it is impossible of define an upper bound function which inverse is also the upper bound of the sensitivity function. The Nyquist curves of the controlled systems of the models of cluster $C1$ are presented in figures 14-15.
Figure 10: Frequency response of the closed-loop systems of cluster $C_1$. The centroid model is represented in black.

Figure 11: Frequency response of the open-loop controlled systems of cluster $C_1$. The centroid model is represented in black.
Figure 12: Frequency response of the transfer function from the reference to the control action of systems of cluster $C_1$. The centroid model is represented in black.

Figure 13: Multiplicative uncertainties with the representation of the sensitivity function for models of cluster $C_1$. The centroid model is represented in black.
Figure 14: Nyquist curves of cluster $C_1$. The centroid model is represented in black.

Figure 15: Detail of figure 14.
3.2.2 Cluster \( C_2 \)

For the second cluster \( C_2 \), composed of models \( M_i \), with \( i = 1, 5, 8, 9, 16, 18, 20 \), the choice of the real poles is 0.8 and the observer polynomial root is 0.99, leading to the following polynomials of the closed-loop transfer function

\[
A_m = z^4 - 3.2000 z^3 + 3.8400 z^2 - 2.0480 z + 0.4096 \quad (28)
\]

\[
B_m = 8.2271 \times 10^{-4} z^3 + 7.7729 \times 10^{-4} z^2, \quad (29)
\]

The controller for cluster \( C_2 \) is defined by polynomials

\[
R_{C_2} = z^4 - 3.3432 z^3 + 4.1660 z^2 - 2.3011 z + 0.4783 \quad (30)
\]

\[
S_{C_2} = -0.0401 z^4 + 0.0740 z^3 + 0.0061 z^2 - 0.0740 z + 0.0340 \quad (31)
\]

\[
T_{C_2} = -0.0135 z^4 + 0.0267 z^3 - 0.0132 z^2. \quad (32)
\]

Figure 16 shows the time responses and frequency responses where the models in cluster \( C_2 \) are controlled with its respective nominal controller. It is possible to infer that the controller is stable for all models (figure 18) although it is not possible to define the upper bound for the multiplicative uncertainties (figure 20). The closed-loop transfer function from the reference to the control action presented in figure 19, shows amplification in gain for high frequencies, that may induce to oscillatory modes for all models. The Nyquist curves of cluster \( C_2 \) are presented in figures 21-22.
Figure 17: Frequency response of the closed-loop systems of cluster C2. The centroid model is represented in black.

Figure 18: Frequency response of the open-loop controlled systems of cluster C2. The centroid model is represented in black.
Figure 19: Frequency response of the transfer function from the reference to the control action of systems of cluster $C_2$. The centroid model is represented in black.

Figure 20: Multiplicative uncertainties with the representation of the sensitivity function for models of cluster $C_2$. The centroid model is represented in black.
Figure 21: Nyquist curves of cluster $\mathcal{C}2$. The centroid model is represented in black.

Figure 22: Detail of figure 21.
3.2.3 Cluster C3

The third cluster C3 is formed by models $M_i$, with $i = 2, 10, 12, 17$ with centroid model $M_{17}$. The controller is designed with poles 0.92 and observer polynomial root 0.97, and the resulting polynomials of the desired closed loop transfer function are defined as

\[
A_m = z^4 - 3.6800z^3 + 5.0784 z^2 - 3.1148 z + 0.7164 \quad \text{(33)}
\]

\[
B_m = 2.0742 \times 10^{-5} z^3 + 2.0218 \times 10^{-5} z^2, \quad \text{(34)}
\]

The controller is defined by polynomials

\[
R_{C3} = z^4 - 3.6954 z^3 + 5.1193 z^2 - 3.1521 z + 0.7282 \quad \text{(35)}
\]

\[
S_{C3} = -0.0308 z^4 + 0.0586 z^3 + 0.0029 z^2 - 0.00586 z + 0.0273 \quad \text{(36)}
\]

\[
T_{C3} = -0.0018 z^4 + 0.0035 z^3 - 0.0017 z^2. \quad \text{(37)}
\]

In figure 23, cluster C3 time responses show similar behaviors except for model $M_{12}$ (red). This model also shows amplification at certain frequencies in closed-loop (figures 24 and 26). The stability condition is verified for all models, in figure 25. This controller presents positive multiplicative uncertainties as well, and it is not possible to determine an upper bound (figures 27). The Nyquist curves of cluster C3 are presented in figure 28-29.

![Figure 23: Time response and control action simulations, with Simulink® , of the controller defined for cluster C3. The centroid model is represented in black.](image_url)
Figure 24: Frequency response of the closed-loop systems of cluster C3. The centroid model is represented in black.

Figure 25: Frequency response of the open-loop controlled systems of cluster C3. The centroid model is represented in black.
Figure 26: Frequency response of the transfer function from the reference to the control action of systems of cluster C3. The centroid model is represented in black.

Figure 27: Multiplicative uncertainties with the representation of the sensitivity function for models of cluster C3. The centroid model is represented in black.
Figure 28: Nyquist curves of cluster C3. The centroid model is represented in black.

Figure 29: Detail of figure 28.
4 Conclusion

The impossibility to determine the upper bound function for the multiplicative uncertainties as well as for the sensitivity function leads to the conclusion that these controllers do not hold the robust stability condition and, therefore, are not robust for the respective models of the clusters. This method, as described, is not suitable for finding a controller robustly stable with appropriate responses for these models.
References


## Appendix B

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

<table>
<thead>
<tr>
<th>$\gamma$ (l$^{-1}$)</th>
<th>$k_{11}$ (s$^{-1}$)</th>
<th>$k_{12}$ (s$^{-1}$)</th>
<th>$k_{21}$ (s$^{-1}$)</th>
<th>$k_{22}$ (s$^{-1}$)</th>
<th>$k_{23}$ (s$^{-1}$)</th>
<th>$k_{30}$ (s$^{-1}$)</th>
<th>$C_{\text{prop}}^{\text{i}}$ µg.ml$^{-1}$</th>
<th>$C_{\text{remi}}^{\text{i}}$ µg.ml$^{-1}$</th>
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