Model identification for control of patients subject to general anesthesia

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Chapter 1

Model Sensitivity and Parameter Estimation

Sensitivity analysis has the objective of studying how the variation of a system parameter affects its output. The sensitivity of the output, as well as the state, with respect to the parameters of the model of a dynamic system, depends on time. It is given by a function that satisfies a differential equation. It is useful to find such a function since this allows to find the time instants in which a parameter has its greatest effect, i.e., in which data is more informative about the parameters to estimate.

If a small change in a parameter results in relatively large changes in the output, the output is said to be sensitive to that parameter. If parameters have a small sensitivity, they are hard to estimate since a small deviation does not induce an evident change in the response of the system.

In this chapter the equations satisfied by the sensitivity are obtained, first in the general case, and then, as an illustrative example, in the case of the logistic equation. Since the logistic equation depends only on two parameters, the quadratic cost used to identify them may be plotted in perspective to provide visual insight. This is done for costs obtained with different sets of data points, corresponding to time epochs in which the sensitivity to the various parameters is different. In this way, we establish a link between sensitivity and the cost used for identification, using sampling instants.

1.1 Sensitivity equations

Consider the model described by:

\[ \dot{x} = f(x, u, \theta) \]  
\[ y(t, \theta) = h(x(t, \theta), \theta) \]

where \( \theta \in \mathbb{R}^n \) is a vector of parameters to estimate, \( x \in \mathbb{R} \) is the state, \( y \in \mathbb{R} \) is the observed variable, \( u \in \mathbb{R} \) is the manipulated variable and \( f \) and \( h \) are smooth functions.

Let \( \theta_0 \) denote the time value of the parameter vector.

Through the Taylor expansion of the function \( y(t, \theta) \) with respect to \( \theta \) and around a point \( \theta_0 \), and ignoring terms of order greater than 1, we obtain:

\[ y(t, \theta) \approx y(t, \theta_0) + \frac{\partial y}{\partial \theta}(\theta - \theta_0) \] (1.3)

That is

\[ \frac{\partial y}{\partial \theta} \approx \frac{y(t, \theta) - y(t, \theta_0)}{(\theta - \theta_0)} \] (1.4)

Define the deviation of \( y \), for computed using a perturbed value \( \theta \) of the parameter, with respect to the "true" value \( \theta_0 \), as:
\( \delta y = y(t, \theta) - y(t, \theta_0) \) \hspace{1cm} (1.5)

And the deviation of \( \theta \) as:
\[ \delta \theta = \theta - \theta_0 \] \hspace{1cm} (1.6)

The sensitivity of \( y \) to the parameters \( \theta \) is defined as:
\[ S_{\theta} = \left[ S_{\theta_1}, S_{\theta_2}, \ldots, S_{\theta_{n_p}} \right]^T = \frac{\partial y}{\partial \theta} = \left[ \frac{\partial y}{\partial \theta_1}, \frac{\partial y}{\partial \theta_2}, \ldots, \frac{\partial y}{\partial \theta_{n_p}} \right]^T \] \hspace{1cm} (1.7)

Where \( n_p \) is the number of parameters.

Therefore, by the above definition of sensitivity, it is concluded that equation (1.4) is a numerical solution for the sensitivity of the parameters in \( \theta \).

On the other side, if we derive equation (1.1) with respect to a given parameter \( \theta_j \), we obtain that:
\[ \frac{\partial}{\partial \theta_j} \dot{x}(t, \theta) = \frac{\partial f}{\partial x} \frac{\partial x}{\partial \theta_j} + \frac{\partial f}{\partial \theta_j} u(t) \] \hspace{1cm} (1.8)

or, changing the order of derivatives:
\[ \frac{d}{dt} \left( \frac{\partial x}{\partial \theta_j} \right) = \frac{\partial f}{\partial x} \frac{\partial x}{\partial \theta_j} + \frac{\partial f}{\partial \theta_j} \] \hspace{1cm} (1.9)

From the definition of sensitivity, \( S_j = \frac{\partial x}{\partial \theta_j} \), as we saw in equation (1.7), it is possible to write equation (1.9) as:
\[ \frac{d}{dt} S_j = \frac{\partial f}{\partial x} S_j + \frac{\partial f}{\partial \theta_j} \] \hspace{1cm} (1.10)

This differential equation should be integrated together with (1.1, 1.2) to provide the required values for \( x \) in (1.1). It is also remarked that the sensitivity depends, in general, on the manipulated variable \( n \).

### 1.2 A particular case: Wiener Model

Consider a system modeled by a Wiener Model. This kind of models consists of a dynamic linear system followed by a static nonlinearity.

Let the linear part of the model be described by the following continuous linear system of state equations:
\[ \dot{x}(t, \theta) = A(\theta)x(t, \theta) + B(\theta)u(t) \] \hspace{1cm} (1.11)
\[ x_n(t, \theta) = Cx(t, \theta) \] \hspace{1cm} (1.12)

where \( A \) and \( B \) are matrices of suitable dimension, and \( C=[1 0 0 \ldots 0] \). Of course, \( C \) may in general depend on \( \theta \). This particular choice is considered because it corresponds to anesthesia models that will be explored later.

The non-linear part is described by:
\[ y(t, \theta) = h(x_1(t, \theta), \theta) \] \hspace{1cm} (1.13)

Figure 1.1 shows the block diagram of the Wiener Model.

To obtain the sensitivity, derive equation (1.11) with respect to a general parameter \( \theta_j \):
\[ \frac{\partial}{\partial \theta_j} \dot{x}(t, \theta) = \frac{\partial}{\partial \theta_j} (A(\theta)x(t, \theta)) + \frac{\partial B(\theta)}{\partial \theta_j} u(t) \] \hspace{1cm} (1.14)
or, interchanging the order of derivatives,

\[
\frac{d}{dt} \frac{\partial x}{\partial \theta_j}(t, \theta) = \left( \frac{\partial}{\partial \theta_j} A(\theta) \right) x(t, \theta) + A(\theta) \frac{\partial}{\partial \theta_j} x(t, \theta) + \frac{\partial B}{\partial \theta_j} u(t) \tag{1.15}
\]

From the definition of sensitivity, \( S_j(t) = \frac{\partial x(t, \theta)}{\partial \theta_j} \), it is possible to write equation (1.15) as:

\[
\frac{d}{dt} S_j(t) = \frac{\partial}{\partial \theta_j} A(\theta) x(t, \theta) + A(\theta) S_j(t) + \frac{\partial B}{\partial \theta_j} u(t) \tag{1.16}
\]

Applying the variation of constants formula to equation (1.16), yields the following explicit formula for the computation of the sensitivity of the state of a linear model:

\[
S_j(t) = e^{A(\theta)t} \int_0^t e^{A(\theta)(t-\sigma)} \left[ \frac{\partial A(\theta)}{\partial \theta_j} x(\sigma, \theta) + \frac{\partial B(\theta)}{\partial \theta_j} u(\sigma) \right] d\sigma \tag{1.17}
\]

It is remarked that, in most practical situations the sensitivity is obtained by the numerical solution of (1.16), instead of using the explicit formula (1.17).

Differentiating now (1.13) with respect to a parameter \( \theta_j \):

\[
\frac{\partial}{\partial \theta_j} y(t, \theta) = \frac{\partial h}{\partial x_1} \frac{\partial x_1}{\partial \theta_j} + \frac{\partial h}{\partial \theta_j} \Leftrightarrow \frac{\partial}{\partial \theta_j} y(t, \theta) = C \frac{\partial x}{\partial \theta_j} + \frac{\partial h}{\partial \theta_j} \tag{1.18}
\]

From the definition of sensitivity, equation (1.14), it is possible to write equation (1.18) as:

\[
S_{yj} = CS_j + \frac{\partial h}{\partial \theta_j} \tag{1.19}
\]

that represents the sensitivity of the output \( y \) with respect to the parameter \( \theta_j \).

### 1.3 Example: Logistic Equation

In order to illustrate the computation of the sensitivity using the formulas obtained in Section 1.1 and to illustrate the relationship between sensitivity, the instants of sampling and the cost, consider the continuous system described by the logistic equation:

\[
\dot{x} = Kx \left( 1 - \frac{x}{M} \right) \tag{1.20}
\]

where \( \theta = [KM]^T \) is a vector of parameters to estimate.

In order to simulate this system, a block diagram was constructed through the use of SIMULINK and MATLAB, as illustrated in Figure 1.2.
1.3.1 Sensitivity Analysis

In order to draw the sensitivity curves of the model parameters K and M, by applying equation \(1.10\), the following system of differential equations is obtained:

\[
\begin{align*}
\frac{dx}{dt} &= K x \left(1 - \frac{x}{M}\right) \\
\frac{dS_K}{dt} &= K \left(1 - \frac{2x}{M}\right) S_K + x \left(1 - \frac{x}{M}\right) \\
\frac{dS_K}{dt} &= K \left(1 - \frac{2x}{M}\right) S_K + \frac{Kx^2}{M^2}
\end{align*}
\]  

(1.21)  
(1.22)  
(1.23)

Figure 1.3 shows the block diagram of the system represented by equations \(1.21\)–\(1.23\). The sensitivity of the parameters was also found numerically using equation \(1.4\). The same results were obtained for the both methods, as expected.

In Figure 1.4 it is possible to see both the model representation for the "optimal" K and M, both the
sensitivity curves of K and M. As seen, the sensitivity of K is maximum between 2.5 and 3.5 days while the sensitivity of M starts to increase only after 3 days. Also, the sensitivity of K is higher than the sensitivity of M, which means that a small deviation in K will cause a higher change than a small deviation of M would cause in the output of the system.

Figure 1.4: The blue curve represents the model, the green curve the sensitivity of parameter K and the red curve the sensitivity of parameter M.

1.3.2 Effect on the Cost Function

Let $x$ be the vector containing the experimental values in the time instances $t = 1, 2, ..., 5$, and $\hat{x}$ the vector with the numerical solution of the differential equation in the same time instances. The deviations vector is given by:

$$\varepsilon = x - \hat{x}(\theta) \quad (1.24)$$

and the sum of the square of the deviations, $J$, by:

$$J = \sum_{1}^{N} \varepsilon_i^2 = \varepsilon^T \varepsilon \quad (1.25)$$

Afterwards, several experiments were taken into account in order to try a normalization of the contour lines of $J$, putting them more rounded, to turn the identification easier.

Three other models were constructed. One of them only considered the points in a certain relevant zone (the rising zone), as represented by the red line in Figure 1.5.

Figure 1.5: The blue curve represents the first model and the red line the model containing only the points of the zone of interest. Both the models have a K value of 2.15 and a M value of 49.33.

The other model was identified using the points in the beginning, from day 1 to day 2. The last one used the points at the end, from day 4 to day 5.
The cost function $J$ was computed for all data sets and the results were compared. The obtained mesh and contour plots are shown in Figure 1.6. 

The minimum is the same in the three curves, as expected. However, some differences are noticed. Comparing the first with the second row of Figure 1.6, we realize that there is a loss of sensitivity of $K$. In the third row, there is a huge loss of sensitivity of $M$, which is concordant with Figure 1.4. On the other side, in the last row, there is huge loss of sensitivity in $K$, which is also concordant with Figure 1.4.

It is also concluded that it is not possible to do a normalization of the contour lines by considering only some relevant points of the model under consideration.
Figure 1.6: The left figures are the mesh representations of $J$ in function of $K$ and $M$. The figures on the right are the contour lines of $J$. The first row of figures represents the first model data, the second one represents the red model of Figure 1.5, the third one is the model containing only the initials points and the fourth is the model containing only the final points.
Chapter 2

Neuromuscular Blockade Model in Anesthesia

Anesthesia involves three important actions for the patient: Neuromuscular Blockade (for keeping the patient still), Depth of Anesthesia (DoA), for inducing a desired level of loss of consciousness, and analgesia (in order to reduce the response to noxious stimuli). This chapter presents the results obtained for the sensitivity of each parameter of the Neuromuscular Blockade (NMB) model.

Drug dosing can be studied by using pharmacokinetic (PK) and pharmacodynamic (PD) modeling. PK is the study of the concentration of drugs in tissue as a function of time and dose. PD is the study of the relationship between drug concentration in plasma and drug effect. Considering PK, i.e. the relationship between dose and the resultant plasma drug concentration, and PD, i.e. the relationship between concentration and effect, a model of drug dosing can be constructed.

The dynamic response of the NMB induced by a bolus (i.e., a sudden infusion performed with a syringe) of atracurium may be modeled as shown in figure 2.1 by a pharmacokinetic/pharmacodynamic (PK/PD) model that has a Wiener structure.

The input is the drug infusion rate and the output is the blockade level, measured in a normalized way between 0% (full paralysis) and 100% (normal muscle activity).

The standard model of anesthesia is presented as well as a minimally parameterized model.

2.1 NMB standard model

In order to write the equations that model NMB, let \( y = r \) be the blockade level, \( u \) the drug infusion rate \( u(t) [\mu gkg^{-1}min^{-1}] \), \( x = [x_1 x_2 x_3 x_4]^T \) the state, with \( x_4 [\mu gml^{-1}] \) the drug concentration in the effect compartment, the plasma concentration \( c_p(t) [\mu gml^{-1}] \) being

\[
c_p(t) = x_1(t, \theta) + x_2(t, \theta)
\]

and

\[
\theta = [\lambda_1 \lambda_2 \lambda a_1 a_2 \tau C_{50} \gamma]^T
\]

Figure 2.1: Structure of the pharmacokinetic/pharmacodynamic NBM.
a vector of patient dependent parameters. The units are: $a_1$ and $a_2$ [kg/ml$^{-1}$], $\lambda_1$, $\lambda_2$ and $\lambda$ [min$^{-1}$], $\tau$ [min], $C_{50}$ [mg/ml$^{-1}$] and $\gamma$ dimensionless.

Model equations consist of a linear dynamic part

$$\dot{x}(t, \theta) = A(\theta)x(t, \theta) + B(\theta)u(t)$$

(2.3)

and a nonlinear output equation described by

$$y(t, \theta) = h(x(t, \theta), \theta)$$

(2.4)

The parameter dependent matrices in (2.3) are:

$$A(\theta) = \begin{bmatrix}
-\lambda_1 & 0 & 0 & 0 \\
0 & -\lambda_2 & 0 & 0 \\
\lambda & \lambda & -\lambda & 0 \\
0 & 0 & \frac{1}{\tau} & -\frac{1}{\tau}
\end{bmatrix}$$

(2.5)

and

$$B(\theta) = \begin{bmatrix}
a_1 \\
a_2 \\
0 \\
0
\end{bmatrix}$$

(2.6)

The function $h(x(t, \theta), \theta)$ of the output equation (2.4) is given by the Hill equation

$$h(x(t, \theta), \theta) = \frac{100C_{50}^\gamma}{C_{50}^\gamma + x_4^\gamma(t, \theta)}$$

(2.7)

### 2.2 NMB minimally parameterized model

Mainly due to the high number of parameters to be identified in the standard model (section 2.1), a new minimally parameterized model for the NMB was proposed in [1].

In frequency domain, the linear dynamics of the NMB minimally parameterized model is given in continuous-time by

$$Y_a(s) = \frac{\alpha}{s + \alpha} \frac{k_1\alpha}{s + k_1\alpha} \frac{k_2\alpha}{s + k_2\alpha} U_a(s),$$

(2.8)

where $Y_a(s)$ is the Laplace transform of the continuous-time output $y_a(t)$ of the model linear dynamic block and $U_a(s)$ stands as in section 2.1. Here the patient-dependent parameter is $\alpha$. The parameters $k_i$, $\{i = 1, 2\}$ are chosen to be constant in 4, and 10, respectively [2].

The static nonlinearity is the same as in the standard model

$$y(t) = \frac{100C_{50}^\gamma}{C_{50}^\gamma + (y_a(t))^{\gamma}},$$

(2.9)

where $\gamma$ is also a patient-dependent parameter that adapts the shape or static differential gain of [2.6].

The parameter $C_{50}$ is chosen to be constant [2] and $y(t)$ is the output of the nonlinearity, the NMB.

The total number of parameters that characterizes each individual’s NMB response in the minimally parameterized model is hence two.

Since no general database of parameters for the minimally parameterized model has been published until the writing of this report, identification methods have to be used to obtain nominal values of the parameters in those models. The Prediction Error Method (PEM) proposed in [2] was used. Let the parameter vector $\theta$ in the minimally parameterized models be split in

$$\theta = [\theta_l^T \theta_n^T]^T,$$

(2.10)

where $\theta_l$ has the parameters from the linear part of the Wiener model and $\theta_n$ has the parameters present in the nonlinearity.
In general lines, the PEM determines $\theta$ (2.10) so that the prediction error
$$\varepsilon(t, \theta) = y(t) - \hat{y}(\theta_n, \hat{y}(t, \theta_l))$$
becomes as small as possible. Note that $y(t)$ is the measured output (NMB or BIS) and $\hat{y}(\theta_n, \hat{y}(t, \theta_l))$ is the predicted output based on the parameter vector $\theta$.

The negative gradient $\psi(t, \theta)$ of the prediction error $\varepsilon(t, \theta)$ with respect to the parameter vector that is needed to the PEM algorithms is given by
$$\psi(t, \theta) = \left[ \frac{\partial \varepsilon(t, \theta)}{\partial \theta} \right]^T = \left[ \frac{\partial \hat{y}(\theta_n, \hat{y}(t, \theta_l))}{\partial \theta} \right]^T = \left[ \frac{\partial \hat{y}(\theta_n, \hat{y}(t, \theta_l))}{\partial \theta} \right]^T \left( \frac{\partial \hat{y}(\theta_n, \hat{y}(t, \theta_l))}{\partial \theta} \right)^T$$

The criterion to be minimized in the search, $V(\theta)$, is
$$V(\theta) = \frac{1}{N} \sum_{t=1}^{N} \varepsilon^2(t, \theta),$$
where $N$ is the total number of data points.

The minimization of (2.13) is performed using the numerical Newton-Raphson algorithm, $\theta^{(k+1)} = \theta^{(k)} - \beta \left( V''(\theta^{(k)}) \right)^{-1} V'(\theta^{(k)})^T$,

where $\theta^{(k)}$ denotes the $k$th iteration in the search and $\beta$ is a diagonal matrix used to control the step length. The derivatives of $V(\theta)$ can be found as:
$$V'(\theta) = -\frac{2}{N} \sum_{t=1}^{N} \varepsilon^T(t, \theta) \psi^T(t, \theta),$$
$$V''(\theta) = \frac{2}{N} \sum_{t=1}^{N} \psi(t, \theta) \psi^T(t, \theta) - \frac{2}{N} \sum_{t=1}^{N} \varepsilon^T(t, \theta) \frac{\partial}{\partial \theta} \psi^T(t, \theta)$$
$$\approx \frac{2}{N} \sum_{t=1}^{N} \psi(t, \theta) \psi^T(t, \theta) .$$

The approximation in (2.16) is justified in [3] and is supported by the fact that, at the global minimum point, $\varepsilon(t, \theta)$ becomes asymptotically white noise which is independent of $\psi(t, \theta)$.

As mentioned in section 2.2, there are two patient dependent parameters in the NMB minimally parameterized model. Since the remaining are constant, they are not considered in the identification step. Hence, for the NMB, the PEM was run in a database of 60 real cases collected in the surgery room [2] and the nominal values of the parameter vector \( \theta \) with $\theta_1 = \alpha$ and $\theta_n = \gamma$ were obtained, forming the new database $P = \{P_i(\theta_i)\}, \{i = 1, \ldots, 60\}$ of nominal values for the parameters in the NMB minimally parameterized model.

For consistency purposes it is important to assess sensitivity and identifiability properties of both the patient-dependent parameters and the ones that were chosen to be constant among patients. The results of such assessment may either support the choices that were made in [1] and [3] or point to improvements or changes regarding the parameters that have been considered to span the patient dynamic variability of behaviors and that were consequently identified in the referred works.

The parameter vector $\theta$ for the sensitivity and identifiability assessment of the NMB minimally parameterized model stands as
$$\theta = [k_1 \ k_2 \ \alpha \ C_{50} \ \gamma]^T.$$
2.3 Sensitivity Analysis

The sensitivity analysis relates the perturbation on parameters to the effect induced in the output of the system. Let $\theta_0$ be the vector of nominal parameters and $\theta$ the perturbed one. Each of these parameter vectors correspond to a different output, i.e., $y(t, \theta_0)$ and $y(t, \theta)$. The perturbation, $\delta \theta = \theta - \theta_0$, induces thus a perturbation on the output, $\delta y(t) = y(t, \theta) - y(t, \theta_0)$.

Performing a Taylor expansion of $y(t, \theta)$ with respect to $\theta$ and around $\theta_0$, it is seen that, neglecting higher orders, the increments $\delta \theta$ and $\delta y(t)$ are related by:

$$\delta y(t) = S_y(t) \delta \theta$$  \hspace{1cm} (2.18)

where

$$S_y(t) = \frac{\partial y}{\partial \theta} = \left[ \frac{\partial y}{\partial \theta_1}, \ldots, \frac{\partial y}{\partial \theta_{n_p}} \right]$$  \hspace{1cm} (2.19)

is the sensitivity vector of dimension equal to the number of parameters $n_p = 8$. The time dependency of the sensitivity means that the influence of each parameter on the output depends on time. This provides information about the time periods in which data is more significant for identification and that, for each parameter, correspond to the ones in which sensitivity is higher.

From the definition of sensitivity,

$$S_{x,j} = \frac{\partial x(t, \theta)}{\partial \theta_j}$$  \hspace{1cm} (2.20)

and differentiating (2.20) with respect to a generic parameter $\theta_j$, we obtain

$$\frac{\partial}{\partial \theta_j} y(t, \theta) = \frac{\partial h}{\partial x} \frac{\partial x}{\partial \theta_j} + \frac{\partial h}{\partial \theta_j}$$  \hspace{1cm} (2.21)

where $\frac{\partial x}{\partial \theta_j}$ is obtained differentiating (2.3), as it was demonstrated in (1.16).

Since $\frac{\partial h}{\partial x} = \left[ 0, 0, 0, \frac{\partial h}{\partial x_4} \right]^T$, it is possible to simplify (2.21):

$$\frac{\partial}{\partial \theta_j} y(t, \theta) = \frac{\partial h}{\partial x_4} \frac{\partial x_4}{\partial \theta_j} + \frac{\partial h}{\partial \theta_j}$$  \hspace{1cm} (2.22)

Figure 2.2 shows the blockade level and the output sensitivity for the standard model with respect to the parameters defined in (2.2). A zoom of the sensitivity corresponding to some parameters may be seen in Figure 2.3. The sensitivity curves depend on the system input. The blockade level used to plot
the curves in Figure 2.2 corresponds to a situation common in surgery when there is an initial drug bolus that quickly drives the index close to zero. After a time period, that is patient dependent, the level starts to grow due to drug absorption. A constant drug dose per unit time is then administered to the patient in order to keep the relaxation level at 10%.

As it is noticed in Figures 2.2 and 2.3, the periods in which parameters are more sensitive correspond to the descent after the initial bolus and to the growing period of relaxation after the initial drug bolus has been absorbed. This is understandable because these are transient periods that reveal the system dynamics. On the other side, the sensitivities are very low when the blockade level is saturated close to zero.

In Figure 2.3 it is evident that the parameters that correspond to the largest sensitivity are $a_1$ and $a_2$ (of the PK model) and $C_{50}$ (of the Hill equation in the PD model). On the opposite, the output is very little sensitive to parameters $\tau$ and $\gamma$.

As it is shown in Fig. 2.4 the output of the NMB minimally parameterized model is very sensitive to the parameter $\alpha$. From the zoomed plot in Fig. 2.5 and similarly with the NMB standard model, the periods during which parameters are more sensitive correspond to the drop and recovery after the initial bolus. In Fig. 2.4 and 2.5 it is evident that the parameter that correspond to the largest sensitivity is $\alpha$, even though $C_{50}$ and $\gamma$ are also quite sensitive. On the contrary, the output is little sensitive to the parameters $k_2$ and $k_3$.

### 2.4 Local Identifiability

From the sensitivity computation a local identifiability analysis is performed around the nominal value of the parameters. For that purpose, organize the output samples of $y$ into a single column $Y$ and let $\delta Y$ be a perturbation in model output induced by a small parameter perturbation $\delta \theta$. These quantities are related by:

$$\delta Y = S \delta \theta$$ (2.23)

where each column of the matrix of sensitivity $S$ corresponds to $S_y(t)$, as computed in the previous subsection, for a given sampling time instant $t$.

A further step is taken in order to eliminate the effect of parameter scaling. This is done by defining the normalized parameter perturbation

$$\overline{\delta \theta} \triangleq diag(\theta) \delta \theta$$ (2.24)

With this definition it is easy to see that

$$\delta Y = S \overline{\delta \theta}$$ (2.25)
Figure 2.4: Output sensitivity of each parameter of the NMB minimally parameterized model.

Figure 2.5: Output sensitivity of each parameter of the NMB minimally parameterized model (detail).
where the normalized sensitivity $\mathbf{S}$ is given by
\[
\mathbf{S} = \mathbf{S}_{\text{diag}}(\theta) \tag{2.26}
\]
The advantage of combining all the output samples into a single matrix is to allow us to measure if there are linear dependencies between parameters, in which case they are not (locally) identifiable. The rank of the matrix gives us knowledge about the effect of parameter changes in the output. If the sensitivity matrix does not have full rank, then some parameters are unidentifiable because different nonzero combinations of their increments yield the same output increment. In practice, this is evaluated by performing a singular value decomposition of $\mathbf{S}$ (for absolute parameter variations) or $\mathbf{S}$ (for relative parameter variations) and looking at its singular values.

The singular value decomposition of an $m \times n$ matrix $\mathbf{M}$ is a factorization of the form
\[
\mathbf{M} = \mathbf{U} \Lambda \mathbf{V}^T \tag{2.27}
\]
where $\mathbf{U}$ is an $m \times m$ matrix, $\Lambda$ an $m \times n$ diagonal matrix with nonnegative real numbers on the diagonal and $\mathbf{V}$ $n \times n$ matrix.

Figure 2.6 shows the singular values of $\mathbf{S}$ for the NMB standard model. As can be seen, although all identifiable, not all the parameters have equal significance. This conclusion is reached because all the singular values are within a reasonable range. Some of the parameters that correspond to lower singular values, namely 7 and 8, can be fixed \textit{a priori}, reducing the complexity of the identification task and eliminating an useless degree of freedom.

These parameters may be obtained by looking at the eigenvectors of the sensitivity matrix, shown in Table 2.1. The entries of the eigenvector corresponding to singular value 8 are high for parameters that may not be identifiable: $\lambda_1$, $\lambda$, $a_1$ and $a_2$. Assuming that the singular value 7 is also neglected, $\lambda_2$ is also added to the list of potentially unidentifiable parameters.

In order to try to improve the identifiability of the parameters, the model was divided in four others:

1. a model considering the sensitivity across the descending phase of the NMB
2. a model considering the sensitivity across the saturation close to zero phase
3. a model considering the sensitivity across the rising phase of the NMB
Table 2.1: Vectors corresponding to the singular values shown in Figure 2.6

<table>
<thead>
<tr>
<th></th>
<th>1</th>
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<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_1$</td>
<td>$7.048 \times 10^{-4}$</td>
<td>$-1.37 \times 10^{-3}$</td>
<td>$-0.052$</td>
<td>$-0.168$</td>
<td>$-0.602$</td>
<td>$0.720$</td>
<td>$-0.246$</td>
<td>$0.167$</td>
</tr>
<tr>
<td>$\lambda_2$</td>
<td>$-9.317 \times 10^{-4}$</td>
<td>$-0.016$</td>
<td>$0.025$</td>
<td>$0.039$</td>
<td>$0.277$</td>
<td>$-0.104$</td>
<td>$-0.949$</td>
<td>$0.094$</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>$-3.109 \times 10^{-3}$</td>
<td>$0.229$</td>
<td>$0.250$</td>
<td>$-0.150$</td>
<td>$0.142$</td>
<td>$-0.062$</td>
<td>$0.134$</td>
<td>$0.906$</td>
</tr>
<tr>
<td>$\alpha_2$</td>
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<td>$0.202$</td>
<td>$0.245$</td>
<td>$0.121$</td>
<td>$0.641$</td>
<td>$0.658$</td>
<td>$0.107$</td>
<td>$-0.170$</td>
</tr>
<tr>
<td>$\tau$</td>
<td>$2.839 \times 10^{-3}$</td>
<td>$0.327$</td>
<td>$0.393$</td>
<td>$0.792$</td>
<td>$-0.323$</td>
<td>$-0.071$</td>
<td>$-0.049$</td>
<td>$-7.049 \times 10^{-4}$</td>
</tr>
<tr>
<td>$C_{50}$</td>
<td>$0.879$</td>
<td>$0.354$</td>
<td>$-0.317$</td>
<td>$0.014$</td>
<td>$0.019$</td>
<td>$-6.815 \times 10^{-4}$</td>
<td>$-8.207 \times 10^{-3}$</td>
<td>$1.218 \times 10^{-4}$</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>$-0.476$</td>
<td>$0.645$</td>
<td>$-0.594$</td>
<td>$0.040$</td>
<td>$0.029$</td>
<td>$-0.012$</td>
<td>$-0.014$</td>
<td>$2.527 \times 10^{-3}$</td>
</tr>
</tbody>
</table>

Figure 2.7: Singular values of normalized sensitivity matrix $\overline{S}$ for model 1.

4. a model considering the sensitivity across the saturation at 10%

A singular value decomposition of the sensitivity matrix $S$ for each model was performed and it is displayed in Figures 2.7, 2.8, 2.9 and 2.10.

The entries of the eigenvector corresponding to singular values 8 and 7 are high for the same parameters of the model considering the all time instants. Thus, it was concluded that the division of the whole model in the four parts was not relevant for the intended analysis.

Figure 2.11 shows the singular values of the matrix $\overline{S}$ for the NMB minimally parameterized model. From the dispersion of the singular values the two lowest eigenvalues, fourth and fifth, can be negligible. Similarly as before, the parameters corresponding to these lowest singular values can be fixed a priori, reducing the complexity of the identification task. These parameters may be obtained by looking at the eigenvectors of the sensitivity matrix, shown in Table 2.2. The entries of the eigenvector corresponding to singular values number four and five are high for parameters that may not be identifiable: $k_2$ and $k_3$.

These are strong results that validate the choice of reducing the number of parameters in the modeling of the NMB input-output relationship as it was described in [1]. The fact of having not all parameters easily identifiable in the standard model was considered as the driving argument in [1] to propose a minimally parameterized model able to cope with the limited amount of data points in each case study and not rich excitatory pattern of the drug doses inputs. Here a quantitative evidence of the local identifiability properties of the NMB standard model is presented. Moreover, in the minimally
Figure 2.8: Singular values of normalized sensitivity matrix $\overline{S}$ for model 2.

Figure 2.9: Singular values of normalized sensitivity matrix $\overline{S}$ for model 3.
parameterized model, the less identifiable parameters are $k_2$ and $k_3$ which supports the choice of fixing them \( a \) \textit{priori} in the minimally parameterized model as mentioned in section 2.2.

Table 2.2: Vectors \((10^{-1})\) corresponding to the singular values shown in Figure 2.11.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>$k_2$</td>
<td>0.233</td>
<td>2.84</td>
<td>-2.17</td>
<td>9.16</td>
<td>1.82</td>
</tr>
<tr>
<td>$k_3$</td>
<td>0.192</td>
<td>2.07</td>
<td>-2.98</td>
<td>0.502</td>
<td>-9.30</td>
</tr>
<tr>
<td>$\alpha$</td>
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<td>-2.44</td>
<td>1.06</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>6.54</td>
<td>-1.85</td>
<td>6.56</td>
<td>2.41</td>
<td>-2.24</td>
</tr>
<tr>
<td>$C_{50}$</td>
<td>-7.48</td>
<td>-0.0999</td>
<td>6.00</td>
<td>2.04</td>
<td>-1.98</td>
</tr>
</tbody>
</table>
Figure 2.11: Singular values of normalized sensitivity matrix $\mathbf{S}$ for the parameters of the NMB minimally parameterized model.
Chapter 3

Depth of Anesthesia

This chapter presents the results obtained for the sensitivity of each parameter of the DoA model. Since the drug used as analgesic (remifentanil) has a non-negligible effect on DoA, it is taken into account as an accessible disturbance. Thus, hereafter, the remifentanil effect concentration, $c_{\text{rem}}$, is assumed to be given. The drug used to control the DoA is propofol, that is a hypnotic drug. It is known that remifentanil and propofol, when applied together, produce a synergistic effect and their effects are potentiated.

The two drugs interact as it shown in Figure 3.1. They act as independent models in the PK and effect compartment (linear part of the PD model) and only interact in the last block (non-linear part of the PD model).

### 3.1 Model of DoA

This section describes the standard model used to represent DoA for a patient subject to general anesthesia and a minimally parameterized one.

The data used correspond to published results and/or typical values that lead to responses similar to published ones.

#### 3.1.1 DoA standard model

As seen in Figure 3.1, the PK model provides the propofol plasma concentration, $c_{\text{prop}}$, given in $[\mu g/mL]$, from a given infusion dose of propofol, $u$ (so it is the manipulated variable) given in $[\mu g/h]$. A model based on a compartmental approach is used to represent the PK model. According to this approach, the body is assumed to be divided into several compartments. In each compartment the drug concentration is homogeneous and there are exchanges between compartments.

![Figure 3.1: Structure of the DoA model.](image)
Here, a three compartments model is used as it is shown in Figure 3.2, in which the main compartment represents intravascular blood (blood within arteries and veins) and highly irrigated organs (such as heart, brain, liver and kidney). The other two compartments represent muscles, fat and other organs or tissues. The drug is administrated via intravenous through a given propofol infusion rate, so it enters in the main compartment. The drug is then transferred to two peripheral compartments or it is metabolized and eliminated from the body. Drug in the peripheral compartments is considered metabolically inert and it is transferred back to the main compartment with linear kinetics. So, $k_{10}$, $k_{12}$, $k_{21}$, $k_{13}$ and $k_{31}$ represent the transfer coefficients and are taken from the literature [7].

![Figure 3.2: 3-compartments pharmaco-kinetic model](image)

For each compartment a mass $m_i$ (given in $[\mu g]$) of drug is assumed to be present. Therefore, it is considered the following three dimensions state space representation:

$$x_1 = \begin{bmatrix} m_1 \\ m_2 \\ m_3 \end{bmatrix}$$  \hspace{1cm} (3.1)

where $m_1$, $m_2$ and $m_3$ are the masses of the correspondent compartment, and can be described by the state-space model:

$$\begin{cases} \dot{x}_1 = A_1 x_1(t) + B_1 u(t) \\ c_{prop}^p = C_1 x_1 \end{cases}$$  \hspace{1cm} (3.2)

where:

$$A_1 = \begin{bmatrix} -k_{10} - k_{12} - k_{13} & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix}, \quad B_1 = \begin{bmatrix} \frac{10^4}{3600} \\ 0 \\ 0 \end{bmatrix}, \quad C_1 = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}$$

and $v_1$ is computed from the weight of the patient and the coefficient $v_c \ [L/Kg]$ which represents the volume of compartment one per patient unit weight $[Kg]$:

$$v_1 = \text{weight} \times v_c$$  \hspace{1cm} (3.3)

The coefficient $\frac{10^4}{3600}$ in $B_1$ is required because the infusion rate $u(t)$ in given in $[mL/h]$ and the other variables in $[\mu g/s]$. The PD model can be divided into two parts: one linear (the effect compartment) and another nonlinear (the interaction). The linear part only involves propofol and it links the plasma concentration $c_{prop}^p$ to the effect concentration $c_{e}^p$ (given in $[\mu g/mL]$). The non-linear part takes into account both propofol and remifentanil, and links the effect of the concentration of the two drugs with to the DoA.

The linear part can be represented by a state space concentration with one state,

$$\begin{cases} \dot{x}_2 = A_2 x_2 + B_2 c_{prop}^p \\ c_{e}^p = C_2 x_2 \end{cases}$$  \hspace{1cm} (3.4)

where $A_2 = -k_{e0}$, $B_2 = k_{e0}$ and $C_2 = 1$. $k_{e0}$ is a PD coefficient taken from the literature [7]. The non-linear model, which represents the interaction between the two drugs, was developed using the Hill equation [8]. It consists of a static model with two inputs (the remifentanil and propofol effect concentrations, respectively, $c_{e}^{emt}$ and $c_{e}^p$) and one output (the DoA level, called here $y$).
The effect concentration of each drug is normalized by dividing it by the concentration at half of the maximal effect, $C_{50}^{\text{remi}}$ for the remifentanil and $C_{50}^{\text{prop}}$ for the propofol.

$$U_{\text{remi}} = \frac{C_{50}^{\text{remi}}}{C_{50}^{\text{remi}}}, \text{ and } U_{\text{prop}} = \frac{C_{50}^{\text{prop}}}{C_{50}^{\text{prop}}}$$

Moreover, according to [8], in order to not assume a purely additive system, the effect of the drug mixture $U_{\text{prop}} + U_{\text{remi}}$ is normalized by $U_{50}(\theta)$, which is the effect of the drugs combination at ratio $\theta$ compared with the effect of each normalized drug by itself, which is 1 by definition. The ratio $\theta$ of the drugs is defined as:

$$\theta = \frac{U_{\text{prop}}}{U_{\text{prop}} + U_{\text{remi}}}$$

The term $U_{50}(\theta)$ is defined [8] as:

$$U_{50}(\theta) = 1 - \beta \theta + \beta \theta^2$$

where $\beta$ is a given constant.

Therefore, the resulting effect $y$, in terms of the normalized concentrations, is given by the following equation:

$$y = E_{\theta} \left( 1 - \frac{[(U_{\text{prop}} + U_{\text{remi}}) / U_{50}(\theta)]^\gamma}{1 + [(U_{\text{prop}} + U_{\text{remi}}) / U_{50}(\theta)]^\gamma} \right)$$

where $\gamma$ is the steepness of the concentration-response relation.

So, the non-linear equation (3.8) is the Hill equation, used as the interaction model.

### 3.1.2 DoA minimally parameterized model

The minimally parameterized Wiener model describing the joint effect of the hypnotic propofol and the opioid remifentanil in the BIS is characterized here. As explained in [4], a third-order continuous-time model is proposed for the linear dynamics of both propofol and remifentanil.

Propofol linear dynamics is hence modeled in continuous-time by

$$Y_p(s) = \frac{\chi + \frac{d_1 \chi}{s + d_1 \chi} \frac{d_2 \chi}{s + d_2 \chi}}{s} U_p(s),$$

where $Y_p(s)$ is the Laplace transform of the continuous-time output $y_p(t)$ from the linear dynamic block of the model for propofol; $U_p(s)$ is the Laplace transform of the propofol infusion rate $u_p(t)$ (input signal); $\chi$ is a patient-dependent parameter; and the parameters $d_i$, $i = 1, 2$ are chosen to be constant in 9 and 10, respectively.

Remifentanil linear dynamics is similarly modeled in continuous-time by

$$Y_r(s) = \frac{\eta + \frac{l_1 \eta}{s + l_1 \eta} \frac{l_2 \eta}{s + l_2 \eta}}{s} U_r(s),$$

where $Y_r(s)$ is the Laplace transform of the continuous-time output $y_r(t)$ of the linear dynamic block of the model for remifentanil; $U_r(s)$ is the Laplace transform of the remifentanil infusion rate $u_r(t)$ (input signal); $\eta$ is a patient-dependent parameter; and the parameters $l_i$, $i = 1, 2$ are chosen to be constant in 2 and 3, respectively [3].

Using as starting point the standard model [3,8], a new formulation for the nonlinearity was proposed in [4]:

$$y(t) = \frac{y_0}{1 + \left( \frac{u_r(t)}{C_{50r}} + m \frac{u_p(t)}{C_{50p}} \right)}$$

where $m$ and $\zeta$ are patient-dependent parameters and $y_0$ is chosen to be constant in 97.7. $C_{50p}$ and $C_{50r}$ are propofol and remifentanil normalizing constants, respectively, that are also chosen to be constant [4].

From this, the total number of patient-dependent parameters in the DoA minimally parameterized model is four.

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In the clinical practice, population models are applied to infer the DoA response of each patient to a certain drug administration profile. For propofol, the parameters from Marsh [7] or from Schnider [14] are usually used, whereas for remifentanil, the parameters from Minto [11] are commonly applied.

The joint parameter vector $\theta$ for the DoA standard model accounting for the effect of both propofol and remifentanil stands as

$$\theta = [k_{10p}, k_{12p}, k_{13p}, k_{21p}, k_{31p}, k_{eop}, V_{1p}, k_{10r}, k_{12r}, k_{13r}, k_{21r}, k_{31r}, k_{eor}, V_{1r}, C_{50}^{prop}, C_{50}^{remi}, \gamma, \beta, y_0]^T$$

(3.12)

Similarly to NMB, as mentioned, there are four patient-dependent parameters in the DoA minimally parameterized model. Since the remaining are constant, they are not considered in the identification step. Hence, for the DoA, the PEM was run in a database of 23 real cases collected in the surgery room [4] and the nominal values for the parameter vector $[\theta_i]$ with $\theta_l = [\chi, \eta]^T$ and $\theta_h = [m, \zeta]^T$ were obtained, forming the new database $S = \{S_i(\theta_i)\}, \{i = 1, ..., 23\}$ of nominal values for the parameters in the DoA minimally parameterized model.

For consistency purposes, it is important to assess sensitivity and identifiability properties of both the patient-dependent parameters and the ones that were chosen to be constant among patients. The results of such assessment may either support the choices that were made in [1] and [3] or point to improvements or changes regarding the parameters that have been considered to span the patient dynamic variability of behaviors and that were consequently identified in the referred works.

The parameter vector $\theta$ for the sensitivity and identifiability assessment of the DoA minimally parameterized model stands as

$$\theta = [d_1, d_2, l_1, l_2, \chi, \eta, C_{50p}, C_{50r}, m, \zeta, y_0]^T .$$

(3.13)

### 3.2 Sensitivity Analysis

The sensitivity analysis was performed using the method of the differential equations already presented before in equation (2.21). In order to do so, it was required to assemble the state-space equations of the PK model and the ones of the linear part of the PD model. So, a new state-space system is obtained:

$$\begin{align*}
\dot{x} &= \begin{bmatrix}
-k_{10} - k_{12} - k_{13} & k_{21} & k_{31} & 0 \\
-k_{12} & -k_{21} & 0 & 0 \\
-k_{13} & 0 & -k_{31} & 0 \\
-k_{e0} & 0 & 0 & -k_{e0}
\end{bmatrix} x + \begin{bmatrix}
10^4 \\
3600 \\
0 \\
0
\end{bmatrix} u(t) \\
y &= h(x(p, t), p(t))
\end{align*}$$

(3.14)

where $y$ represents the hill equation (3.8).

Since $\frac{\partial y}{\partial x} = [0, 0, 0, \frac{\partial h}{\partial x_i}]^T$, it is possible to simplify (2.21):

$$\frac{\partial}{\partial \theta_j} y(t, \theta) = \frac{\partial y}{\partial x_i} \frac{\partial x_i}{\partial \theta_j} + \frac{\partial h}{\partial \theta_j}$$

(3.15)

The sensitivity curves depend on the system input. The DoA level used to plot the curves in Figure 3.3 corresponds to a situation common in surgery when there is an initial drug bolus of two drugs (propofol and remifentanil) that quickly leads the patient to a loss of consciousness close to 45% of its normal value. After a time period, that is patient dependent, the level starts to slightly rise and fall. A constant drug dose per unit time is then administered to the patient in order to keep the DoA level at about 45%.

Figure 3.3 shows the time-varying sensitivity of the BIS standard model output with respect to the parameter vector in (3.12). A zoom of the sensitivity corresponding to some parameters may be seen in Fig. 3.4. As it can be noticed, the periods in which parameters are more sensitive correspond to the drop and the recovery after the initial bolus. It is evident that the parameters that correspond to the largest sensitivity are $k_{31p}, k_{21p}, k_{10p}, k_{13p}, k_{10r}, k_{21r}$. On the opposite, the output is little sensitive to the parameters $V_{1p}, V_{1r}, C_{50p}, C_{50r}, \gamma, \beta$ and $y_0$. 

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Figure 3.3: DoA level (top) and output sensitivity for the standard model (bottom).

Figure 3.4: Output sensitivity of each parameter of the DoA standard model (detail).
As it is shown in Fig. 3.5, the output of the DoA minimally parameterized model is very sensitive to the parameter \( \chi \), even though \( \eta \), \( C_{50r} \), and \( \zeta \) are also quite sensitive. From the zoomed plot in Fig. 3.6 and similarly with the DoA standard model, the periods during which parameters are more sensitive correspond to the drop and recovery after the initial bolus. It is also noticed that the output is little sensitive to the parameters \( k_2 \) and \( k_3 \).

![Figure 3.5: Output sensitivity of each parameter of the DoA minimally parameterized model.](image)

![Figure 3.6: Output sensitivity of each parameter of the DoA minimally parameterized model (detail).](image)

### 3.3 Local Identifiability

As it was performed for the NMB, also for the DoA a local identifiability analysis was performed around the nominal values of the parameters. For that purpose, the output samples of \( y \) were organized into a single column \( Y \) and let \( \delta Y \) be a perturbation in the model output induced by a small parameter perturbation \( \delta p \). These quantities are related by:

\[
\delta Y = S\delta p
\]  

(3.16)

where each column of the matrix of sensitivity \( S \) corresponds to \( S_y(t) \), as computed in the previous subsection, for a given sampling time instant \( t \).
A further step is taken in order to eliminate the effect of parameter scaling. This is done by defining the normalized parameter perturbation

$$\Delta \delta p \triangleq \text{diag}(p) \delta p$$

(3.17)

With this definition it is easy to see that

$$\delta Y = S \Delta \delta p$$

(3.18)

where the normalized sensitivity $S$ is given by

$$S = S \text{diag}(p)$$

(3.19)

The advantage of combining all the output samples into a single matrix is to allow us to measure if there are linear dependencies between parameters, in which case they are not (locally) identifiable. The rank of the matrix gives us knowledge about the effect of parameter changes in the output. If the sensitivity matrix does not have full rank, then some parameters are unidentifiable because different nonzero combinations of their increments yield the same output increment. In practice, this is evaluated by performing a singular value decomposition of $S$ (for absolute parameter variations) or $S$ (for relative parameter variations) and looking at its singular values.

The singular value decomposition of an $m \times n$ matrix $M$ is a factorization of the form

$$M = U \Lambda V^T$$

(3.20)

where $U$ is an $m \times m$ matrix, $\Lambda$ an $m \times n$ diagonal matrix with nonnegative real numbers on the diagonal and $V$ an $n \times n$ matrix.

Figure 3.7 shows the singular values of normalized sensitivity matrix $S$ for the DoA standard model. From the dispersion of the singular values the two lowest eigenvales, ninth, tenth and eleventh (please see

Figure 3.8 shows the singular values of the matrix $S$ for the BIS minimally parameterized model. From the dispersion of the singular values the two lowest eigenvalues, ninth, tenth and eleventh (please see
Table 3.1: Vectors \((10^{-3})\) corresponding to the singular values shown in Figure 3.7.

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>(k_{10p})</td>
<td>-401</td>
<td>-307</td>
<td>200</td>
<td>-414</td>
<td>-181</td>
<td>-150</td>
<td>34.0</td>
<td>70.4</td>
<td>-379</td>
<td>389</td>
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<tr>
<td>(k_{11p})</td>
<td>-97.9</td>
<td>161</td>
<td>-46.4</td>
<td>364</td>
<td>170</td>
<td>-158</td>
<td>75.4</td>
<td>272</td>
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<td>2.98</td>
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<td>-727</td>
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<td>(k_{18p})</td>
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<td>-2.95</td>
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<td>(k_{19p})</td>
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<td>-431</td>
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<td>(k_{20p})</td>
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<td>4.02</td>
<td>6.37</td>
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<td>1.70</td>
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Table 3.2: Values corresponding to the singular values shown in Figure 3.7.

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Figure 3.8: Singular values of normalized sensitivity matrix $S$ for the parameters of the DoA minimally parameterized model.
Table 3.4 can be negligible. Similarly as before, the parameters corresponding to these lowest singular values can be fixed \textit{a priori}, reducing the complexity of the identification task. These parameters may be obtained by looking at the eigenvectors of the sensitivity matrix, shown in Table 3.3. The entries of the eigenvector corresponding to singular values number 9, 10 and 11 are high for parameters that may not be identifiable: \(k_1\), \(l_1\), \(l_2\), \(C_{50p}\), \(m\) and \(y_0\).

Table 3.3: Vectors \((10^{-3})\) corresponding to the singular values shown in Figure 3.8.

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Table 3.4: Values of the singular values shown in Figure 3.8.

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Chapter 4

Identification and Control of patients subject to general anesthesia

In this chapter only the NMB standard model (Chapter 2 Section 2.1) is considered due to time issues.

The problem to solve consists in estimating the vector of parameters \( \theta \) given the observations \( \{y(.), u(.)\} \) and then to design a controller based on the identified model such that it will track the reference signal for the output system.

Since the NMB and DoA dynamics are described by a linear dynamic model in series with a nonlinear static function, the identification and the controller design will be based on a local model obtained by linearization of the nonlinear static function. The aim is to contribute for automation of anesthesia and, hence, a Personalized component of 4-P Medicine (Predictive, Preventive, Personalized and Participatory).

It was intended to use real clinical data, thus, first of all we looked at the real cases that we had previously obtained in the operating room and inspected which ones were the best to consider for our analysis (that were the ones that didn’t have many acquisition errors). In total we analyzed clinical data for 5 patients subject to general anesthesia.

4.1 System Identification

System identification has the purpose of finding the best parameters for a given model structure to replicate as well as possible the data collected from a known system.

Due to the fact the NMB data is sampled and collected with a time period of 20 seconds, the dynamics will be described by an ARX discrete time dynamic model. The ARX model is described by the following notation:

\[
A(q^{-1})y(t) = B(q^{-1})u(t) + e(t)
\]  

(4.1)

where \( n_a \) is the dimension of the polynomial \( A(q^{-1}) \), \( n_b \) is the dimension of \( B(q^{-1}) \), \( n_k \) is the pure time delay (number of samples before the input affects output of the system), \( e \) is the white noise disturbance term, with \( A(q^{-1}) = 1 + a_1q^{-1} + \cdots + a_{n_a}q^{-n_a} \), \( B(q^{-1}) = b_1 + b_2q^{-1} + \cdots + b_{n_b}q^{-n_b+1} \) and \( q^{-1} \) is the backward shift operator, defined by \( q^{-1}u(t) = u(t-1) \).

The estimation of the coefficients for the ARX model was done using the System Identification Toolbox of Matlab.

The identification method for the ARX model is the least squares method, which is a special case of the prediction error method. The least squares method is the most efficient polynomial estimation method because this method solves linear regression equations in analytic form. Moreover, the solution is unique.
With the purpose of evaluating the identification methodology, the NMB model is parameterized with the values shown in Table 4.1.

Table 4.1: Values of the parameters used for identification and control purposes.

<table>
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</table>

The time response of the NMB model for the initial bolus of 500 $\mu$g followed by an infusion at the time 30 min is represented in Figure 4.1.

Figure 4.1: Bolus followed by drug infusion with a dither signal.

Figure 4.2: Concentration at the effect site.

This drug infusion rate was chosen in order to simulate the manual control of anesthesia. The response was maintained near 10% (after the recovery), and it is in this period that data was obtained for identification.

Since all the data is sampled, it implies that the dynamic part of the model is represented in discrete-time, that is, the relationship between the input system $u(t)$ and the concentration at the effect site $C_e(t)/C_{50}$ is linear. The application of the least square method, with the selection of $n_a = 3$ and $n_b = 2$, to $\{u(t), C_e(t)\}$ gives the result shown on Figure 4.4 that has a good fitting.

The problem here is that biological systems are non-linear (represented by the Hill equation) and ARX model can only be applied to linear systems. Thus, the output of the modeled dynamic system
Figure 4.3: NMB response.

Figure 4.4: Identification of the NMB linear dynamics with access to $C_e(t)$, with $n_a = 3$ and $n_b = 2$. The fitting is 98.63%. The obtained polynomials are: $A(q) = 1 - 2.719q^{-1} + 2.459q^{-2} - 0.7397q^{-3}$ and $B(q) = 8.921 \times 10^{-6}q^{-1} + 2.925 \times 10^{-5}q^{-2}$.
for anesthesia (Hill equation) had to be linearized around a working point (linearization point), \((\bar{u}, \bar{y})\), in order to be possible the application of the ARX modeling. Therefore, the working point was set to be 10% for the NMB model.

The NMB level can thus be expressed as a function of this point:

\[
y = \bar{y} + \delta y(t)
\]  

(4.2)

\(\delta y\) is called the output incremental value.

This point corresponds to the input point:

\[
y = \bar{u} + \delta u(t)
\]  

(4.3)

After the signals \(\delta y(t)\) and \(\delta u(t)\) be computed (see Figure 4.5), the identification software of ARX from Matlab was applied to these signals.

![Figure 4.5: Input and Output signals used to identification.](image)

![Figure 4.6: Measured and simulated model output considering 4 \((n_a = 4)\) poles and 4 \((n_b = 3)\) zeros and nonlinearities. The fitting is 79.89%. The obtained polynomials are: \(A(q) = 1 - 3.696^{-1} + 5.122q^{-2} - 3.156q^{-3} + 0.7294q^{-4}\) and \(B(q) = -0.000286q^{-1} - 0.000676q^{-2} + 0.0006835q^{-3} + 0.0002157q^{-4}\).](image)

As it is shown in Figure 4.6, the fitting using 4 poles and 4 zeros is not perfect but is quite good. Afterwards the modeling was performed with 4 poles and 3 zeros (Figure 4.7) and the result is similar to Figure 4.6. With that, it is possible to conclude that the model on Figure 4.7 replicates the real model as well as the one on Figure 4.6 and is simpler, so the ARX model with \(n_a = 4\), \(n_b = 3\) and \(n_k = 1\) was the one used for identification purposes. In order to investigate whether there are huge changes when the number of poles and zeros are more reduced, it was considered a model with 2 poles and 1 zero (Figure 4.8) and it is possible to see that the difference of the fitting’s percentage is not very different from the other models, which could allow to increase even more the simplification of the model.
Figure 4.7: Measured and simulated model output considering 4 \((n_a = 4)\) poles and 2 \((n_b = 3)\) zeros and nonlinearities. The fitting is 78.9\%. The obtained polynomials are: \(A(q) = 1 - 3.688q^{-1} + 5.114q^{-2} - 3.161q^{-3} + 0.7355q^{-4}\) and \(B(q) = -0.0004637q^{-1} - 0.001014q^{-2} + 0.00133q^{-3}\).

Figure 4.8: Measured and simulated model output considering 2 \((n_a = 2)\) poles and 1 \((n_b = 2)\) zeros and nonlinearities. The fitting is 73.85\%. The obtained polynomials are: \(A(q) = 1 - 1.964q^{-1} + 0.965q^{-2}\) and \(B(q) = -0.0007897q^{-1} - 0.002181q^{-2}\).
4.2 Control

The goal is to control the output of the system as close as possible to the reference signal by manipulating the administration of the drug. Please see the blockade model on Figure 4.9 to get a better perspective.

![Figure 4.9: Blockade model considering a PID controller.](image)

In continuous time, the model of NMB (section 2.1) can be represented by the transfer function

\[
\frac{c_e(s)}{u(s)} = \frac{a_1 s + a_2}{s + \lambda_1 + s + \lambda_2} \frac{\lambda}{s + \lambda s + \tau} \frac{1}{C_{50}}
\]

(4.4)

\[
r(t) = \frac{100}{1 + \left(\frac{c_e}{C_{50}}\right)^\gamma}
\]

(4.5)

Here, the model and the parameters are the same of the previous Section. From the analysis of the models it is possible to conclude that one of the poles is much faster than the others \((\tau >> \lambda_1, \lambda_2)\) and there is a near cancellation of a pole with a zero. Using these facts and rearranging (4.4) it is obtained

\[
\frac{c_e(s)}{u(s)} = \frac{1}{C_{50}} \frac{a_1 \lambda_2 + a_2 \lambda_1}{\lambda_1 \lambda_2} \frac{1}{(\lambda^{-1}s + 1)(\lambda^{-1}s + 1)}
\]

(4.6)

Consider \(K = \frac{1}{C_{50}} \frac{a_1 \lambda_2 + a_2 \lambda_1}{\lambda_1 \lambda_2}\), so equation (4.6) can be written as

\[
\frac{c_e(s)}{u(s)} = \frac{K}{s^2 + \alpha_1 s + \alpha_0}
\]

(4.7)

which admits the following representation

\[
\dot{c}_e(t) + \alpha_1 \ddot{c}_e(t) + \alpha_0 c_e(t) = Ku(t)
\]

(4.8)

It is possible to put the equation above in a state-space representation:

\[
\begin{bmatrix}
\ddot{c}_e \\
\dot{c}_e
\end{bmatrix} =
\begin{bmatrix}
-\alpha_1 & -\alpha_0 \\
1 & 0
\end{bmatrix}
\begin{bmatrix}
\dot{c}_e \\
\dot{c}_e
\end{bmatrix} +
\begin{bmatrix}
0 \\
K
\end{bmatrix} u(t)
\]

(4.9)

\[
c_e = \begin{bmatrix}
0 \\
1
\end{bmatrix}
\begin{bmatrix}
\ddot{c}_e \\
\dot{c}_e
\end{bmatrix}
\]

(4.10)

It is known that the error is the difference between the ideal concentration effect output, \(c_{e0}\), and the actual measured one, \(c_e\), thus it is remarked that

\[
e_1(t) = c_{e0} - c_e(t)
\]

(4.11)

\[
e_\dot{1}(t) = -\ddot{c}_e(t)
\]

(4.12)

\[
e_\ddot{1}(t) = -\dddot{c}_e(t)
\]

(4.13)
Replacing \( e_1 \) in equation (4.15), defining \( u(t) = u_0 - \Delta u(t) \) and knowing that \( c_{e0} = K_{a0} u_0 \), it is obtained
\[
\ddot{e}_1(t) + \alpha_1 \dot{e}_1(t) + \alpha_0 e_1(t) = K \Delta u(t)
\] (4.15)

In this case we consider a nominal concentration effect, \( c_{e0} \), such that the output value is \( r_0 = 10 \) and it’s the controller’s reference.

Consider a linearization around the working point \((r_0, c_{e0})\) and performing a Taylor expansion it is possible to write
\[
r(t) \approx r_0 + K_n (c_e(t) - c_{e0})
\] (4.16)

with \( K_n = \frac{\partial r}{\partial c_e}\bigg|_{c_{e0}} \).

Regarding the controlling purpose, it is intended to manipulate \( u(t) \) such that \( r \rightarrow r_0 \).

By definition, the error of the output, \( e \), is
\[
e(t) = \Delta r_0 - r(t) = K_n (c_e(t) - c_{e0}) = K_n e_1(t)
\] (4.17)

Therefore we can replace \( e_1 \) by \( e \) in equation (4.15) and it becomes
\[
\ddot{e}(t) + \alpha_1 \dot{e}(t) + \alpha_0 e(t) = K_n K \Delta u(t)
\] (4.18)

which admits the following state-space representation:
\[
\begin{bmatrix}
\dot{\hat{e}} \\
\dot{\hat{e}} \\
\hat{z}
\end{bmatrix}
= \begin{bmatrix}
-\alpha_1 & -\alpha_0 & 0 \\
1 & 0 & 0 \\
0 & 1 & 0
\end{bmatrix}
\begin{bmatrix}
\dot{e} \\
e \\
\hat{z}(t)
\end{bmatrix}
+ \begin{bmatrix}
K_n K \\
0 \\
0
\end{bmatrix} \Delta u(t)
\] (4.19)

where the state has the proportional and the differential errors to track the reference signal. Several control strategies can be used to control the NMB response. One of the simplest is the PID control strategy. In order to use it, the model is expanded by including the integral of the error,
\[
z(t) = \int e(h)dh \Rightarrow \dot{z}(t) = e(t)
\] (4.20)

and now the model is represented by
\[
\begin{bmatrix}
\dot{\hat{e}} \\
\dot{\hat{e}} \\
\hat{z}
\end{bmatrix}
= \begin{bmatrix}
-\alpha_1 & -\alpha_0 & 0 \\
1 & 0 & 0 \\
0 & 1 & 0
\end{bmatrix}
\begin{bmatrix}
\dot{e} \\
e \\
\hat{z}(t)
\end{bmatrix}
+ \begin{bmatrix}
K_n K \\
0 \\
0
\end{bmatrix} \Delta u(t)
\] (4.21)

The aim is to manipulate \( \Delta u(t) \) such that \( \dot{e}(t) \rightarrow 0 \) and \( e(t) \rightarrow 0 \). Note that with this explained model and because \( \dot{e}, e \) and \( z \) are accessible variables, a state feedback control can be design such that
\[
\Delta u(t) = - \begin{bmatrix}
K_D & K_P & K_I
\end{bmatrix}
\begin{bmatrix}
\dot{e} \\
e \\
z
\end{bmatrix}
\] (4.22)

which has a structure of a PID controller with the gains \( K_D, K_P \) and \( K_I \) that must be selected. Note that this controller must be equipped with an anti-windup mechanism to bound the value of the integrator.

For the design of the PID controller, the linear quadratic state feedback (LQ) method was used. For a continuous time system, the state-feedback LQ method (1.22) minimizes the quadratic cost function:
\[
J(u) = \int_0^\infty (x^T Q x + u^T R u + 2 x^T N u) dt
\] (4.23)

The matrices \( Q, R \) and \( N \) are tunable parameters, being selected firstly as: \( Q = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \), \( R = 1 \) and \( N = 0 \).
Figure 4.10: Control signal (top) and output of the system after the addition of a PID controller (bottom), with $u_0=0$. Note that only the positive part of the control signal is applied to the system because $u(t)$ must be equal or greater than zero. In this simulation the anti-windup mechanism was not used.

Figure 4.11: Control signal (top) and output of the system after the addition of a PID controller and dividing $K_I$ by 4 (bottom).

Figure 4.12: Control signal (top) and output of the system after the addition of a PID controller and dividing $K_I$ by 10 (bottom).
In Figure 4.10 it is shown the output after a PID controller is added to the system. Since there were a lot of oscillations, $K_I$ was reduced to try to improve the results. In Figure 4.11 it is possible to see that if $K_I$ is divided by 4, the oscillations are quite reduced and when it is divided by 10 (Figure 4.12) the oscillations are almost nonexistent. Manipulations of $K_P$ and $K_D$ were also performed but any better result was obtained. Therefore, it is possible to conclude that by manipulating the gain of the $K_I$ controller it is possible to control pretty well the output of the system. Afterwards, the parameters Q and R of equation (4.23) were manipulated.

![Figure 4.13: Control signal (top) and output of the system after the addition of a PID controller and considering $Q_{33} = 10$ (bottom).](image1)

![Figure 4.14: Control signal (top) and output of the system after the addition of a PID controller and considering $Q_{33} = 0.1$ (bottom).](image2)

It is possible to see that the best results are obtained when $Q_{33} = 0.1$ and $R = 10$ at the same time.
Figure 4.15: Control signal (top) and output of the system after the addition of a PID controller and considering $R = 10$ (bottom).

Figure 4.16: Control signal (top) and output of the system after the addition of a PID controller and considering $R = 0.1$ (bottom).

Figure 4.17: Control signal (top) and output of the system after the addition of a PID controller and considering $Q_{33} = 0.1$ and $R = 10$ (bottom).
Chapter 5

Conclusions

This project analyzes the anesthesia problem in the point of view of identification and control of patients subject to neuromuscular blockade, analgesia and hypnosis.

There were four key aspects in this work. The performance of the sensitivity analysis allowed to know which time periods were more significant for identification (namely immediately after the initial bolus and then after the recovery for both NMB and DoA) as well as for which of the model’s parameters the output is more sensitive. The local identifiability allowed to exclude some of the parameters from the identification task, which made this process simpler. The identification is important to determine the parameters given the observations. The control of the output is a very important step.

This work provides a contribution to the future development of a personalized Medicine.
Bibliography


