Clustering in Supervised Multi-model Adaptive Control Applied to Neuromuscular Blockade *

João M. Lemos ∗ Pedro S. Oliveira** Jorge S. Marques*** Teresa F. Mendonça****

* Universidade Técnica de Lisboa/IST/INESC-ID, Lisboa, Portugal (email: jml@inesc.pt)
** INESC-ID/IST, Lisboa, Portugal (email: pedro.s.oliveira@ist.utl.pt)
*** Universidade Técnica de Lisboa/IST/ISR, Lisboa, Portugal (email: jsm@isr.ist.utl.pt)
**** Faculdade de Ciências da Universidade do Porto, Portugal (email: tmendo@fc.up.pt)

Abstract: This work approaches the problem of forming clusters of linearized models that cover the possible dynamic behavior of neuromuscular blockade of patients subject to anaesthesia. The motivation stands from the design of supervised multi-model adaptive controllers where a group of "similar" models is associated with a single controller. Due to this connection to a control problem, the similarity among models is measured using the $\nu$ gap metric since this ensures that, if two models are close in this norm, then a controller that stabilizes one of the models will also stabilize the other. Two algorithms are proposed for model clustering. The first one starts with an initial classification that relies on insight from the particular problem of neuromuscular blockade control. The other may be used in other applications as well and relies on an initialization based on agglomerative clustering techniques. In both cases, the initial classification is then improved by the $k$-means algorithm.

Keywords: Identification; Classification; Biomedical control; Estimation; Adaptive control.

1. INTRODUCTION

This paper is concerned with the design of supervised switched multi-model adaptive controllers in the situation where the number of controllers is significantly smaller than the number of possible plant models and the application of the algorithms developed to a case study on the control of neuromuscular blockade level in patients subject to general anaesthesia. Hereafter the problem to solve is formulated, the state of the art is concisely reviewed and the paper organization and contributions are summarized.

1.1 Problem formulation

Supervised switched multi-model adaptive control (SMMAC) was conceived in order to improve controller performance in plants with a high level of uncertainty. Designing SMMAC implies the solution of two problems [Anderson et al. 2000a, Anderson et al. 2000b]:

- Finding a set of models $\mathcal{M}$ that "covers" plant dynamic and associate controllers to it;
- Finding a supervisor that is able to select a controller matching one, or one group, of model(s) in $\mathcal{M}$ that stabilizes the closed loop and yields the specified performance.

A number of supervisors based on switching logic may be considered [Morse 1995]. The algorithm considered in this paper uses dwell time switching [Morse 1996].

In what concerns model covering, a formulation that suits the objectives of this work is phrased as follows:

**Problem I:** Consider a set of $N$ linear dynamic models

$$\mathcal{M} = \{M_j = M(P_j), j = 1, \ldots, N\}$$

where $P_j$ represents model parameters. To each model $M_j$ in this set associate a controller $C_k$ such that it stabilizes $M_j$ and all the models $M_i$ that are "close" to $M_j$ in the sense that

$$\rho(M_j, M_i) \leq \gamma$$

where $\rho$ is a suitable distance and $\gamma$ is a constant. Furthermore, the controller performance (as measured, e. g. by the overshoot and settling time) when $C_j$ is applied to any model $M_i$ in the class defined by (1) should be similar. The number of controllers $N_C$ should be $N_C \ll N$.

In order to meet the requirement $N_C \ll N$, it is necessary to make a partition of $\mathcal{M}$ in $N_c$ subsets $\mathcal{M}_k$

$$\mathcal{M} = \bigcup_{k=1}^{N_c} \mathcal{M}_k$$

in a way that models in $\mathcal{M}_k$ will be well regulated by the controller $C_k$, where the bank of controllers is given by

* Part of this work was performed in the framework of project IDEA – Integrated Design for Anaesthesia Automation, financed by FCT Portugal under contract PTDC/EEA-ACR/69288.
The advantage of reducing the number of controllers amounts to a void excessive switching among controllers corresponding to models that correspond to similar dynamics. This is expected to improve the controlled system’s performance.

This paper presents clustering algorithms to find the model sets $\mathcal{M}_k$, $k = 1$ Independent, $\mathcal{N}_C$ in the partition of $\mathcal{M}$ that rely on two types of approaches:

- Using insight from the specific plant to control, do a first partition and then refine it using pattern classification methods ($k - means$ algorithm) [Duda et al. 2001].
- Obtain an initial partition using agglomerative graph algorithms [Duda et al. 2001, Jain et al. 1999] and then refine it as in the previous approach.

Following [Anderson et al. 2000a], the metric $\rho$ is the $\nu$ – gap metric introduced in [Vinnicombe 1993].

The system to control is the neuromuscular blockade level in patients subject to general anaesthesia, for which a set of 100 models representative of possible patient dynamics is available [Lemos et al. 2005].

1.2 State of the Art

The idea of switched control is not new, dating back from 40 years ago, but it was the concept of ”supervisor”, together with progress in Robust Control, that lead to an increasing interest on its adaptive capabilities. A supervisor is a subsystem that orchestrates the switching of candidate controllers so as to achieve some prescribed specifications [Morse 1995]. Besides the major problem of stability [Morse 1996, Narendra and Balakrishnan 1997, Branicki 1998, Angeli and Mosca 2002], alternative supervisory design methods receive a continuous attention [Anderson et al. 2000b, Mosca and Agnoloni 2001].

SMMAC has been applied to the control of neuromuscular blockade (NMB) in [Lemos et al. 2005]. Although this work reports actual clinical cases, PIDs are used as local controllers and the number of controllers equals the number of models. In [Mendonça et al. 2007] the influence of the observer polynomial when controlling NMB with SMMAC is studied and again demonstrated on clinical cases. The possibility of using on NMB a supervisor relying on controller falsification with a reduced number of controllers is studied in [Agnoloni et al. 2005].

1.3 Paper contributions and organization

The main contribution of this paper consist on the development of algorithms for solving the model clustering problem in SMMAC in a systematic way, using Pattern Recognition methods, and their application to the neuromuscular blockade control problem.

The paper is organized as follows: After the Introduction (this section) in which the problem to solve is formulated, the state of the art reviewed and the paper contributions

Fig. 1. Block diagram of the neuromuscular blockade model.

and organization stated, the relevant aspects of the dynamics of NMB are presented on section 2. The essentials of supervised multi-model adaptive control for the work reported here are described in section 3. The core of the paper consists of section 4, devoted to model clustering. Section 5 reports results on control of NMB using variants of the model clusters obtained in the previous section and, finally, section 6 draws conclusions.

2. THE DYNAMICS OF NEUROMUSCULAR BLOCKADE

A patient subject to general anaesthesia must be medicated with drugs to induce three different effects: Loss of consciousness, insensitivity to noxious stimuli (“pain”) and areflexia (“lack of movement”) achieved through neuromuscular blockade (NMB). The availability of fast acting non-depolarizing drugs affecting neuromuscular transmission allows the control of NMB [Asbury and Linkens 1986]. These drugs include atracurium, mivacurium and rocuronium among others [Appiah-Ankum and Hunter 2004].

The dynamic response of the neuromuscular blockade for atracurium may be modeled [Weatherley et al. 1983, Lemos et al. 2005] using a compartmental model, resulting in the Wiener type model shown in Figure 1. Here, the linear pharmacokinetic model with transfer function

\[ G_{PK}(s) = \frac{a_1}{\tau_1 s + 1} + \frac{a_2}{\tau_2 s + 1} \]  \hspace{1cm} (2)

relates the drug infusion rate $u(t)$ [\(\mu g kg^{-1} min^{-1}\)] with the plasma concentration $c_p(t)$ [\(\mu g ml^{-1}\)], where $a_i$, expressed in [\(\mu g ml^{-1} min^{-1}\)] and $\tau_i$ [min] ($i = 1, 2$) are patient dependent parameters.

The pharmacodynamic part comprises a linear model that relates the plasma concentration with the so called effect concentration $c_e(t)$, described by the transfer function

\[ G_{PD}(s) = \frac{1}{(\tau_3 s + 1)(\tau_4 s + 1)} \]  \hspace{1cm} (3)

and a nonlinear static relation between the effect concentration and the NMB level $r(t)$ [%], assumed to be given by the Hill equation, written as

\[ r(t) = \frac{100 C_{50}^0}{C_{50}^0 + c_e(t)} \]  \hspace{1cm} (4)

where parameters $\tau_i$ [min] ($i = 3, 4$), $C_{50}^0$ [\(\mu g ml^{-1}\)] and $\gamma$ (dimensionless) are also patient-dependent. The variable $r(t)$, normalized between 0 and 100, measures the level of the neuromuscular blockade, 0 corresponding to full paralysis and 100 to full muscular activity.

Fig. 2 shows the typical response to a drug bolus (i.e. a sudden injection) of the PK/PD model explained above. After some delay due to the drug diffusion in the body...
Fig. 2. Typical NMB response to a bolus with the features $T_{10}$, $T_{50}$ and $P$ indicated.

(modeled by the real poles of the linear part of the PK/PD model), the effect concentration $C_e$ starts to grow and the NMB level drops quickly to a value below 5% where it stays for a period. As the drug is eliminated by the body, the NMB level grows then to recover the value of 100% if no further drug is administered.

3. SUPERVISED MULTI-MODEL ADAPTIVE CONTROL

Figure 3 shows the basic architecture employed by the supervisory multi-model adaptive control (SMMAC) structure. It consists of a bank of $N_c$ controllers and a supervisor. The supervisor decides at each time what is the index $\phi$ of the controller to actually apply to the plant (the patient). This decision is based on a multiple model based estimator that compares the outputs of a bank of models with the actual plant output. The index of the model that best fits the observed plant dynamics is then used to select the controller to apply.

The original approaches used as many controllers as models. It is also possible to associate each controller to a class of models, thereby reducing excessive switching that would lead to performance degradation.

Although other switching strategies would be possible [Morse 1995], in order to ensure stability, a dwell time condition [Morse 1996] is used in the work reported in this paper. This amounts to impose that, once a controller is applied to the plant, it will remain so for at least a minimum period of time (the dwell time).

Fig. 4 shows the supervisor structure. The model bank used as a basis for the multi-estimator is made from $N$ models $M_j$, each represented by the ARX model

$$A_j(q^{-1})y_j(t) = B_j(q^{-1})u(t)$$

in which $u$ and $y$ are incremental plant’s input and output and

$$A_j(q^{-1}) = 1 + \sum_{i=1}^{n_a} a_j_i q^{-i} \quad B_j(q^{-1}) = \sum_{i=1}^{n_b} b_j_i q^{-i}$$

are polynomials in the unit delay operator $q^{-1}$, with $A_j$ (monic) and $B_j$ of fixed degrees $n_a$ and $n_b$ respectively, for all $j = 1, \ldots, N$ and $t$ is discrete time. These models are obtained from the linearization of a discrete time version of the the Wiener NMB model described in section 2. From each model $j$ from the bank, the output estimator assuming $M_j$ to hold true is given by

$$\hat{y}_j(t) = (A_j^o - A_j) \frac{1}{A_j^o} y(t) + B_j \frac{1}{A_j^o} u(t).$$

where $A_j^o(q^{-1}) = 1 + \sum_{i=1}^{n_a} a_o_i q^{-i}$ is a monic hurwitz polynomial with the same degree as the $A_j$’s, that will hereafter be referred as the prediction observer polynomial.

For the prediction of each model $M_j$, a prediction error $e_j$ is then computed by

$$e_j(t) = \hat{y}_j(t) - y(t)$$

and the performance index $\pi_{pj}$ by

$$\pi_{pj}(k) = \lambda_p \pi_{pj}(k-1) + (1-\lambda_p) e_j^2(k),$$

where $\lambda_p$ is a parameter that can be either constant or variable. The variable solution aims at adjusting $\lambda_p$ as a function of a measure of the input excitation according to the following rationale: when the control error (it could be the prediction error as well) is below a specified threshold, the adaptation is suspended and $\lambda_p$ is set to $\lambda_0 = 0.85$ which implies faster adaptation.

Each controller $C_i$ in the bank of controllers is designed by pole placement, using a polynomial approach [Aström and Wittenmark 1997] and has the structure

$$R^i(q)u(t) = T^i(q)r^i(t) + S^i(q)r(t)$$

where $R^i(q)$, $S^i(q)$ and $T^i(q)$ are polynomials in the forward-shift operator $q$ and $r_c$ is the reference to track.

4. MODEL CLUSTERING

The association of groups of models to a single controller must be done in such a way that each controller not only stabilizes the closed-loop resulting from all the models in the corresponding class, but also yields a similar performance as measured, e. g., by the settling time, overshoot
and acceptable values of the manipulated variable. For that sake, whenever a distance is needed in the model clustering procedure in order to define a distance between two linear models, the $\nu - gap$ distance is used. This ensures that, if two models are close enough in this sense, a controller that stabilizes one will also stabilize the other. Furthermore, for each class of models one has to adjust the predictor and observer polynomials.

Two main approaches are described hereafter for model clustering:

- Problem dependent approach.
- Graph algorithm based approach.

### 4.1 Problem dependent approach

This approach is based on insight on the problem and "manual" choices made on the space of features. An initial classification is then refined using the $k$-means algorithm. For this sake, the space with the two features $T_{10}-T_{80}$ and $P$ defined in figure 2 is considered. The quantity $T_{10} - T_{80}$ is the time for the bolus response of the NMB to drop from 80% to 10% and $P$ is the time the response stays below 5%.

Fig. 5 shows the location of all the 100 models considered in the space of these features, as well as their partition in 7 classes. The dashed lines in red represent the class separation and the * are the centroids, chosen such that the controller designed based on them stabilizes every model in the class. Since, as can be observed in this figure, there are very dense areas, the corresponding clusters have been refined. This new partition, with 12 classes, is shown in figure 6.

Both these initial partitions are then modified using a modification of the $k$-means algorithm [Duda et al. 2001] that is suitable for the problem at hand. This algorithm reads as follows:

**Modified $k$-means Algorithm.**

Recursively execute the following steps:

**Step 1. Initialization.**

For each of the classes $C_i$, $i = 1, \ldots, N_c$ select a model $M_i$ that will be taken as a centroid for class $C_i$.

**Step 2. Reclassification**

Reclassify all the models $M_i$, $i = 1, \ldots, N$ by attributing them to the class $C_k$ such that $\delta_{\nu}(C_k, M_i)$ is minimum. Here, $\delta_{\nu}$ denotes the $\nu - gap$ distance.

**Step 3. Centroid actualization.**

For each class $C_k$, $k = 1, \ldots, NC$ find the new centroid as the model $M_k$ among all the models in the class such that $\Sigma_{i \in I_k} \delta_{\nu}(M_k, M_i)$ where $I_k$ denotes the set of indexes of the models in class $C_k$.

**Step 4. Iteration.**

If the termination criteria (either maximum number of iterations completed or convergence achieved) is not fulfilled go to step 2. Otherwise stop.

Figure 7 shows a bank model of NMB responses to a bolus grouped in 7 clusters, obtained using the method described in this section.

### 4.2 Complete Link Algorithm

Due to the fact that it relies on specific problem insight and, in particular, on the visualization of model scattering in a 2-dimensional space, the method described in the previous section may not be used for more complex problems (i.e., when the space of features has dimension higher than 2).

In order to formalize the problem, consider a set of models ("data points") $\mathcal{M} = \{ M_i \in \mathbb{R}^n, i = 1, \ldots, N \}$. Suppose we want to split $\mathcal{M}$ into $N_C$ disjoint subsets (clusters) $\mathcal{M}_1, \ldots, \mathcal{M}_{N_C}$ in such a way that all the points belonging to the same cluster $\mathcal{M}_i$ are close to each other, according to the $\nu - gap$ distance. In practice, the number of clusters is usually unknown and has to be estimated. The estimation of the clusters $\mathcal{M}_i$ from the data set $\mathcal{M}$ or from the matrix of distances is known as a data clustering problem and several methods have been proposed to solve it (e.g., see [Duda et al. 2001, Jain et al. 1999]).
Each method makes its own assumptions about the problem, e.g. by adopting a parametric model for the data or by choosing a suitable cost functional. This work uses the Complete Link algorithm (CL) to perform this task since it only requires the matrix of distances between pairs of "points" (models) that is known in this problem. Furthermore, the CL algorithm tries to find isotropic clusters according to this distance that seems to be a reasonable assumption to associate "data points" (models in this application). It is remarked that the distance used in this problem is not induced by an Euclidean norm.

The CL algorithm initializes the set of clusters, considering \( N_C \) different clusters i.e., each data point belongs to a different cluster. Then the algorithm merges the pair of closest clusters. The distance between two clusters \( \mathcal{M}_i \) and \( \mathcal{M}_j \) is defined as the diameter of the union set \( \mathcal{M}_i \cup \mathcal{M}_j \), given by

\[
d(\mathcal{M}_i, \mathcal{M}_j) = \max_{x, y \in (\mathcal{M}_i \cup \mathcal{M}_j)} \delta_v(x, y) \quad (10)
\]

where \( \delta_v \) denotes the \( v \)-gap distance between models \( x \) and \( y \).

The merging step is repeated \( N \) times until all the points belong to the same cluster. Therefore, the complete link algorithm provides a sequence of clustering solutions starting with \( N \) clusters and ending with a single cluster. The algorithm may of course be stopped between these two extremes to obtain a solution with a pre-specified number of clusters \( N_C \) or a pre-specified diameter. This can also be done using a model selection criterion (e.g., BIC, MDL) to automatically compute the number of clusters.

The CL algorithm is not a fast algorithm since the computation of the closest clusters to be merged is time consuming if thousands of data points are to be processed. Fortunately, this is not a problem in this case. In this problem, the CL algorithm proved to be adequate. Indeed, the controller bank resulting from the initialization of \( k - \text{means} \) by CL leads to a performance that, although lower than the one of section 4.1, is still acceptable. Section 5 provides a quantitative comparison.

Fig. 7. Bank model of NMB responses to a bolas grouped by clusters. The method applied considers 7 classes and uses modified \( k - \text{means} \) applied to an initialization made using the problem dependent method.

Fig. 8. Simulation results obtained for \( M_{69} \) with \( \lambda_0 = 0.85 \) and \( \epsilon_c(t) \) threshold of 0.1%. (a) - NMB signal (b) - manipulated variable (c) - switching (\( \sigma \)) and class index (\( \phi \)) signals.

Fig. 9. Simulation results obtained for \( M_{69} \) with \( C_{34} \). Left - NMB signal. Right - manipulated variable.

Fig. 10. Example with observation noise. Left: NMB signal and reference; Right: Manpulated variable.

5. CONTROL RESULTS

An exhaustive simulation study of the performance achieved when SMMAC is applied to a bank of 100 patient models has been made. The results are shown in table 1. The column tagged "Converging cases" indicates the number of cases in that the controller selected is the one of the cluster to which the patient model belongs. Although this is not essential to yield a stabilizing controller, or even good performance, it is a sign of consistency and, therefore, is considered to be desirable. The other indexes include the overshoot [\%] (a measure of the quality of the transient), the settling time \( t_s \) and the mean square tracking error.
Table 1.

<table>
<thead>
<tr>
<th>Control System</th>
<th>converging cases</th>
<th>Overshoot [%]</th>
<th>( t_s ) [min]</th>
<th>MSE [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>avg worst case</td>
<td>avg worst case</td>
<td>avg worst case</td>
<td>avg worst case</td>
</tr>
<tr>
<td>intuitive-7</td>
<td>63</td>
<td>2.84 35</td>
<td>65.22 96</td>
<td>0.0205 0.34</td>
</tr>
<tr>
<td>k-means-7</td>
<td>69</td>
<td>2.25 35</td>
<td>66.65 298</td>
<td>0.3098 29.3</td>
</tr>
<tr>
<td>agglomerative-7</td>
<td>26</td>
<td>23.41 99</td>
<td>110.82 300</td>
<td>11.47 114</td>
</tr>
<tr>
<td>intuitive-12</td>
<td>14</td>
<td>7.09 45</td>
<td>112.07 300</td>
<td>0.7415 8.75</td>
</tr>
<tr>
<td>k-means-12</td>
<td>8</td>
<td>4.25 50</td>
<td>86.47 300</td>
<td>0.6008 15.9</td>
</tr>
<tr>
<td>agglomerative-12</td>
<td>20</td>
<td>9.51 64</td>
<td>107.7 300</td>
<td>1.5882 17.6</td>
</tr>
</tbody>
</table>

in response to a constant reference (MSE). As seen on the table, the purely “Intuitive” method with 7 classes or refined with \( k \) – means are the best methods.

Figure 8 shows the results obtained when controlling \( M_{\theta9} \), one of the most difficult models to control. Figure 9 shows the same patient model controlled with an \textit{a priori} chosen controller. This example illustrates the advantage of embedding adaptation in the controller with respect to the situation in that a single controller aims to be applied to all possible patient models.

Finally, figure 10 shows a result with observation noise.

6. CONCLUSIONS

The problem of associating models in SMMAC in such a way that each model cluster corresponds to one controller has been solved by pattern classification methods. Two algorithms are proposed that differ in the initialization phase. In one case the initialization relies on insight on the NMB level control problem. In the other, the initialization is made using a graph algorithm that is problem independent.

While the second algorithm lead to a lower control performance, it may be applied to problems where one cannot resort to heuristic insight, e. g. because of the high dimension of the space of features.

REFERENCES


