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Controller Falsification in Automatic Drug Delivery for Neuromuscular Blockade Control

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Abstract— **The paper studies the application of a Controller Falsification test for the supervision of automatic drug delivery for neuromuscular blockade control. The purpose is to ensure a suitable control performance by discarding unsuitable candidate controllers for the patient under operation. The insensitivity of the test to the reference amplitude can be exploited by testing the candidate controllers in the loop with a reduced, less invasive, drug infusion.**

I. Introduction

Biological systems are non-stationary and nonlinear, and present a high degree of interindividual variability. Therefore, the control of physiological variables is characterized by a very high degree of uncertainty in the systems' dynamics, while the nature of the application involved requires a very reliable and robust control system.

A general requirement in anesthesia is to ensure a suitable level of muscle relaxation in the patient. Thus, from a control engineering viewpoint, such a requirement can be considered as a regulation problem where the plant to be regulated is the patient, the output is the patient's neuromuscular blockade level $[\%]$ and the input is the drug (Atracurium) infusion rate. In practice the problem is a complicated one, mainly because of undesirable transients caused by the initial ignorance on the relevant patient dynamics.

II. Controller Falsification

Controller Falsification (CF) [4] deals with the problem of finding criteria according to which a higher level control unit, the *supervisor*, decides whether the acting controller is adequate or not to the actual operating conditions. This is a binary decision problem: if the controller is falsified [5] , the supervisor replaces the formerly acting controller with a different one selected amongst the available family of candidate controllers. Controller falsification is made possible through the continuous monitoring of the feedback loop performance and should in principle be sensitive to poor tracking performance, poor transients and loss of stabilization (incipient divergence). The adopted approach considers a data-based statistic (or residual) in the form of a ratio of closed loop variables. In order to consolidate the main ideas underlying the approach, we shall restrict to a SISO linear plant $\mathcal{P}(\theta)$ in discrete-time described in terms of a finite-difference equation

$$\mathcal{P}(\theta) : A_\theta(d)y(t) = B_\theta(d)\delta u(t) + A_\theta(d)w(t) \qquad (1)$$

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where $y(t)$ is the output, $\delta u(t)$ the input-increment, $w(t)$ the output disturbance, $A_\theta(d)$ and $B_\theta(d)$ two polynomials

$$\begin{aligned} A_\theta(d) &= \Delta(d)a(d) = 1 + a_1 d + \ldots + a_{n_a} d^{n_a} \\ \Delta(d) &= 1 - d \\ B_\theta(d) &= b_1 d + \ldots + b_{n_b} d^{n_b} \end{aligned} \qquad (2)$$

where d denotes the unit backward-shift operator, $dy(t) = y(t-1)$, and $\theta \in \Theta \subset \mathbb{R}^{n_\theta}$ an uncertain parameter-vector. Let $\theta := [a_1 \cdots a_{n_a}\ b_1 \cdots b_{n_b}]'$ where the prime denotes transpose. Along with the family of processes (1), consider a one-degree of freedom linear controller

$$\mathcal{C} \ : \ R(d)\delta u(t) \ = \ -S(d)\,[y(t) - r(t)] \qquad (3)$$

where $R(d)$ and $S(d)$ are coprime polynomials in d. Let the feedback control system (1) and (3) be denoted by $(\mathcal{P}(\theta)/\mathcal{C})$, and the following subsets of Θ defined as follows:

$\mathcal{S}$: $= \{\theta \in \Theta : (\mathcal{P}(\theta)/\mathcal{C})$ is stable$\}$;

$\mathcal{D}$: $= \{\theta \in \mathcal{S} : (\mathcal{P}(\theta)/\mathcal{C})$ behaves satisfactorily$\}$;

$\mathcal{S}^c$: the complement of $\mathcal{S}$ in Θ.

Let $r(t)$ be a piecewise constant reference and $\tilde{y}(t) := y(t) - r$ the tracking error. Denoted $\theta^\circ \in \mathcal{D}$ the *nominal* value of the uncertain parameter-vector in (1), let:

$$A^\circ(d) := A_{\theta^\circ}(d) \qquad B^\circ(d) := B_{\theta^\circ}(d)$$

Then,

$$\mathcal{M}^\circ : \quad A^\circ(d)\tilde{y}(t) = B^\circ(d)\delta u(t) \qquad (4)$$

will be called the (deterministic) *nominal model* of the plant. It follows that the *output prediction error* based on $\mathcal{M}^\circ$ is given by

$$\varepsilon(t) := A^\circ(d)\tilde{y}(t) - B^\circ(d)\delta u(t) \qquad (5)$$

Our aim is to monitor the operating loop behavior in order to possibly detect performance degradation. The idea is to compare a ratio of closed loop variables, collected on line as in Fig. 1, with a suitably chosen threshold. Let $z(t) := [\tilde{y}(t) \quad \delta u(t)]'$ and

$$\chi_\theta(d) := A_\theta(d)R(d) + B_\theta(d)S(d)$$

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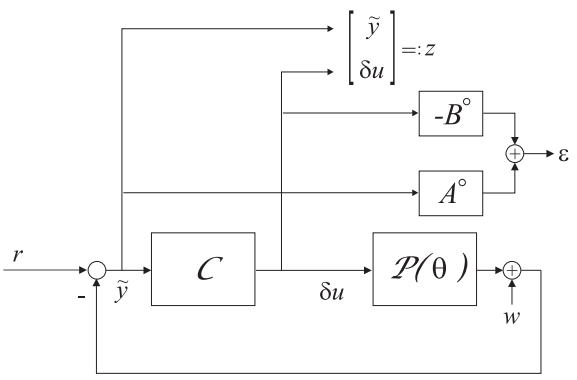

Fig. 1. Closed loop variables collected from the operating loop.

be the characteristic polynomial of the operating feedback-loop $(\mathcal{P}(\theta)/\mathcal{C})$. It can be found that, for $r \equiv const$

$$z(t) := \frac{A_\theta(d)}{\chi_\theta(d)} \begin{bmatrix} R(d) \\ -S(d) \end{bmatrix} w(t) \tag{6}$$

and

$$\varepsilon(t) = \frac{A_\theta(d)\chi^\circ(d)}{\chi_\theta(d)} w(t) \tag{7}$$

with $\chi^\circ(d) = \chi_{\theta^\circ}(d)$. Then, the following relation between closed loop variables holds

$$z(t) := \frac{1}{\chi^\circ(d)} \begin{bmatrix} R(d) \\ -S(d) \end{bmatrix} \varepsilon(t) \tag{8}$$

Notice that the transfer function in (8) is stable by construction ($\chi^\circ(d)$ strictly Schur). Consequently boundedness of $\varepsilon(\cdot)$ implies boundedness of $z(\cdot)$. Denoted $n = \max(n_a, n_b)$, let $\varphi(t) := [\tilde{y}(t-1)\dots\tilde{y}(t-n) \;\; -\delta u(t-1)\dots-\delta u(t-n)]'$. Consider the statistical test

$$g(t) := \frac{1}{n^{1/2}} \frac{\|\varphi(t)\|}{\max|\varepsilon|^t} \begin{matrix}(\leq)\\(>)\end{matrix} T \tag{9}$$

$\max|\varepsilon^t| := \max_{t_0\leq k\leq t}|\varepsilon(k)|$, in order to discriminate between the two mutually exclusive hypothesis $h_{\bar{F}} := \{\theta \in \mathcal{D}\}$ and $h_F := \{\theta \in \mathcal{S}^c\}$, t_0 being the time at which $\mathcal{C}$ is switched on in feedback with $\mathcal{P}(\theta)$. The threshold T should be designed, provided that it is possible (see Theorem 1 in [4] for details), in such a way that

$$P_D(T) := \mathbb{P}\{g(t) > T, \text{ some } t \in [t_0, \infty) | h_F\} = 1$$

$$P_{FA}(T) := \mathbb{P}\{g(t) > T | h_{\bar{F}}\} \simeq 0$$

where $\mathbb{P}\{Q\}$ stands for probability of the event Q, and P_D and P_{FA} denote probability of detection of faults and, respectively, probability of false alarms. For the statistic ratio $g(t)$ in (9) it can be estabilished that [4]

$$g(t) \begin{matrix}\leq_{\mathbb{P}}\\ >_{\mathbb{P}}\end{matrix} \begin{matrix} M_{\varphi/\varepsilon}(\mathcal{D}) \\ \overline{T}\end{matrix} \begin{matrix}\text{if } \|\varphi(\cdot)\| \text{ bounded}\\ \text{if } \|\varphi(\cdot)\| \text{ unbounded}\end{matrix} \tag{10}$$

$$M_{\varphi/\varepsilon}(\mathcal{D}) := \max_{\theta\in\mathcal{D}} \frac{\sqrt{\left|\frac{A_\theta(d)R(d)}{\chi_\theta(d)}\right|_1^2 + \left|\frac{A_\theta(d)S(d)}{\chi_\theta(d)}\right|_1^2}}{\left|A_\theta(d)\frac{\chi^\circ(d)}{\chi_\theta(d)}\right|_1} \tag{11}$$

$$\overline{T} := \left[\max_{\theta\in\mathcal{S}^c} \|\theta - \theta^\circ\|\right]^{-1} \tag{12}$$

where we use the notation "$|x| \leq_{\mathbb{P}} |y|$" if $\mathbb{P}(|x| < \alpha|y|, \; \alpha > 1) \simeq 1$ and $|H|_1$ denotes l_1-norm, *viz.* the l_∞-induced norm of the linear map represented by the transfer function H, *viz.* if $\nu(t) = H(d)v(t)$, $|H|_1 := \max_{\|v(\cdot)\|_\infty=1} \|\nu(\cdot)\|_\infty$. Here it is assumed that $t \geq \tau_D$ where τ_D is so large that

$$\frac{\lambda_\circ^{\tau_D}}{\max|\varepsilon|^{\tau_D}} \ll 1 \tag{13}$$

with $\lambda_\circ \in [0, 1)$ the spectral radius of $\chi^\circ(d)$ in such a way that the test is not affected by the loop transient. In the same way analytical or experimental computation of the threshold T are related to the loop performance in stationary state. In particular, (10) ensures that, if $\|\varphi(t)\|$ diverges, the statistic $g(t)$ must be greater than the number $\overline{T}$, precomputable from the problem parameters. One of the important features of the test is that, being expressed as a ratio of closed-loop variables, it turns out to be insensitive to the noise intensity. This allows one to choose the threshold, irrespective of the noise intensity. Notice here that it is assumed that $\mathbb{P}\{|w(t)| > 0\} = 1$, in particular $w(t)$ could be an intentionally injected white noise acting as a dither in order to provide the required excitation to the loop for the test evaluation. Once again, the noise insensitivity feature of the test is crucial as the dither intensity can be chosen arbitrarily small without affecting the test detection capability. Bounds (11) and (12) can be computed analytically or, for less conservative results, via simulations by computing the test variable $g(t)$ for values of θ varying over the whole uncertainty set.

Remark Consider the statistic

$$g(t; N) = \frac{1}{(nN)^{1/2}} \frac{\left(\sum_{k=0}^{N-1} \|\varphi(t-kn)\|^2\right)^{1/2}}{\max|\varepsilon|^t} \tag{14}$$

$N = 1, 2, \dots$ It is immediate to see that the same conclusions as for $g(t) = g(t; N = 1)$ hold true for $g(t; N)$, $N \geq 1$, whenever $\theta \in \mathcal{S}$. However, (14) has some advantages over $g(t)$. Among the others [4] if $\theta \in \mathcal{S}$ the following $2-$norm approximation holds

$$g(t; N) \cong \frac{\left|A_\theta \frac{\chi^\circ}{\chi_\theta}\mathcal{L}^\circ\right|_2}{\max|\varepsilon|^t} \leq \frac{\left|A_\theta \frac{\chi^\circ}{\chi_\theta}\mathcal{L}^\circ\right|_2}{\left|A_\theta \frac{\chi^\circ}{\chi_\theta}\right|_2} = \left|\overline{A_\theta \frac{\chi^\circ}{\chi_\theta}}\mathcal{L}^\circ\right|_2$$

$$|\mathcal{L}^\circ|^2 := \left|\frac{R}{\chi^\circ}\right|^2 + \left|\frac{S}{\chi^\circ}\right|^2 \tag{15}$$

where: the approximation is in an *a.s.* sense and the bigger N the tighter; for a stable transfer function $H(d)$, $|H|_2^2 := \frac{1}{2\pi}\int_{-\pi}^{\pi} \left|H(e^{j\omega})\right|^2 d\omega$ and $\overline{H} := H/|H|_2$. □

III. CF IN NEUROMUSCULAR BLOCKADE CONTROL

Automatic drug delivery offers the opportunity of safer, more effective and more efficient drug infusion. In particular, it will permit anesthesiologists to better control the effects of modern anaesthetic drugs. Because of low safety margins, the consequences of overdosing can be catastrophic, while under-dosing anaesthetic drugs risks patient awareness and unsuitable conditions for surgery. As advances in pharmacology have resulted in shorter acting neuromuscular blocking agents, the rapid control of dosing becomes more important.

The problem of regulating a patient's neuromuscular blockade level through the infusion of muscle relaxant is a complicated one mainly because of the wide variability of the input output map of the plant which depends on the physiological characteristics of the patient. In fact, a large variability of the patients' response to the same drug administration regime have been observed. Thus, a continuous monitoring of the feedback-loop behavior obtained with the operating controller turns out to be crucial in order to guarantee safety. To this end the described controller falsification statistic has been tested on the setting up of reduced complexity multiple model switching control [1] in order to verify its ability to promptly detect wrong controller selection and poor feedback loop performance.

It is given a family of N dynamic responses of neuromuscular blockade, here $N = 100$ can be considered representative [1] of an exhaustive range of clinical situations. Hence, the family of clinical models is:

$$\mathcal{M} = \{M_j = M(\theta_j), j = \underline{100}\} \tag{16}$$

where $\underline{n} := \{1, \ldots, n\}$,

$$\theta = [a_1 \;\; a_2 \;\; \lambda_1 \;\; \lambda_2 \;\; \lambda \;\; C_{50} \;\; S \;\; \tau]' \in \mathbb{R}^8 \tag{17}$$

the prime denotes transpose and θ is the model-parameter vector whose first 7 elements are patient-dependent and the last is included to better fit clinical data to model. M_j is the cascade connection between a linear system:

$$t(s) = \frac{c_e(s)}{u(s)} = \frac{1/\tau}{s + 1/\tau} \frac{\lambda}{s + \lambda} \left(\frac{a_1}{s + \lambda_1} + \frac{a_2}{s + \lambda_2} \right)$$

followed by a nonlinear memoryless output function:

$$r(t) = \frac{100 C_{50}^S}{C_{50}^S + c_e(t)^S}$$

In these former equations $c_e(t)$ is the effect compartment concentration, $u(t)$ is the drug infusion rate and $r(t)$ is the level of neuromuscular blockade, normalized between 0 and 100, 0 corresponding to full paralysis and 100 to full muscular activity. It is known by previous literature on the subject [2] that, given M_j, a suitably tuned PID controller K_j is as follows:

$$u(nT_s) = g_c \left(1 + \frac{T_s}{c_i} \frac{z}{z-1} + \frac{c_d}{T_s} \frac{z-1}{z} \right) e(nT_s)$$

where $u(t)$ is the atracurium infusion rate, $e(t) = r_0(t) - r(t)$ is the difference between the desired level and respectively the induced level of neuromuscular blockade. T_s is the sampling time and the controller parameters are:

$$\begin{aligned} g_c &= \frac{1.2}{RL} \frac{1}{r_d(r_0)} \\ c_i &= 2L \\ c_d &= L/2 \end{aligned} \tag{18}$$

where $r_d(r_0)$ is the partial derivative of $r(t)$ evaluated at the target value r_0. Then, each model $M(\theta_j)$ is associated to a controller $K(\gamma_j)$, where $\gamma_j = [g_c \;\; L] \in \mathbb{R}^2$ is the controller-parameter vector. In the reduced-complexity setting up a proper partition of the uncertainty interval for g_c and L is used in such a way that only 5 different *barycentric controllers* $\{\mathcal{C}_i, i = \underline{5}\}$ (instead of 100 model based different controllers) are used to cover the whole patients' variability region (see [1] for details).

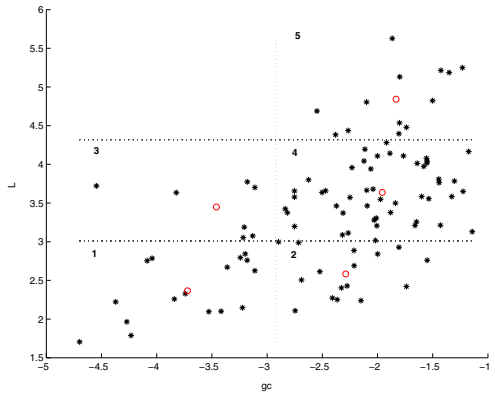

Fig. 2. Partition of the controller parameters space in 5 regions and corresponding *barycentric* controllers (circles). Asterisks represent the projection of the 100 models on such a space.

Here the control task is to let the output $r(t)$ track the "reference" $r_0(t)$. The latter is fixed to a constant value of 10% which corresponds to a high level of neuromuscular blockade typically required in many surgical activities.
Typical clinical procedures consist of injecting an initial bolus of atracurium to the patient in order to induce total neuromuscular blockade in a short time (Fig. 3).

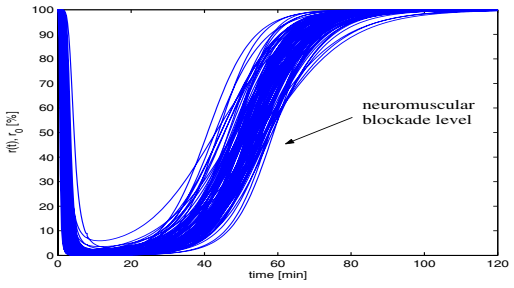

Fig. 3. Simulated induced neuromuscular blockade responses for a bolus of $500\mu g \;\; kg^{-1}$ of atracurium for the N models.

Application of the Controller Falsification test to the described problem presents some interesting aspects for its peculiarities, namely:

- nonlinearity of the plant
- normalization of the output between 0 and 100
- saturation of the controller output for $u < 0$ as only positive infusion rates of drug are allowed

which, though not complied with the theory presented in Sect. 2 make it an interesting empirical application as a performance monitoring and falsification test.

Then, though the computation of the analytical bounds in (11) (as $\theta = \{\theta_j, \ \ j \in \underline{100}\}$ varies over the family of clinical models linearized around the reference value) gives values in good agreement with the experimental results, these are only significant in order to apply the test in stationary regime. Moreover as the nonlinearity in the models introduces a normalization of the output between 0 and 100, here the task is not a "divergence detection" one as every candidate loop is stable, but a "poor performance detection" task. In particular simulation experiments reveal a wide variability in the performance of (patient/controller) loops in terms of transient response, settling time and tracking error which are well caught by the test, though no divergence trend takes place.

Then, more generally, a wider interpretation of the test variable (9) is considered here in order to apply the test as a performance test, even before the transient has exhausted. In fact, notice from the $2-$norm approximation in (15) that $g(t;N)$ provides a normalized measure of the mixed-sensitivity of the operating loop, where the normalization w.r.t. the prediction error has the effect of making the measure insensitive to the (unaccessible) disturbance. Then, low $g(t)$ corresponds to low mixed-sensitivity and can be interpreted as a "well-tuned" index, while $g(t)$ becomes higher getting far from tuning. As the following equality can be verified

$$A_\theta \frac{\chi^\circ}{\chi_\theta} = A^\circ \left[\widetilde{\mathcal{P}} \frac{A_\theta S}{\chi_\theta} + 1 \right]$$

with $\widetilde{\mathcal{P}} := (B^\circ/A^\circ - B_\theta/A_\theta)$ the plant/model distance, (15) can be rewritten as follows

$$g(t;N) \leq \left| \overline{A^\circ \left[\widetilde{\mathcal{P}} \frac{A_\theta S}{\chi_\theta} + 1 \right] \mathcal{L}^\circ} \right|_2$$

while, for the tuned-loop

$$g^\circ(t;N) \leq \left| \overline{A^\circ} \mathcal{L}^\circ \right|_2$$

This makes clear the dependency of the discrepancy of $g(t;N)$ from $g^\circ(t;N)$ on the distance $\widetilde{\mathcal{P}}$ between the actual plant and the model on which the controller under test is tuned; moreover, as the term $A^\circ \mathcal{L}^\circ(e^{j\omega})$ has a typical high pass behavior in control systems, such a discrepancy has a more significant effect as the distance between the models is large at low and moderate frequencies *i.e* in the useful frequency band.

Here it is shown an example where given a patient, ($\mathcal{P}(30)$ in the assigned data set, lying in region 4 according to the distribution in Fig. 2), controllers $\mathcal{C}_1$ and, respectively, $\mathcal{C}_4$ are applied to regulate the drug infusion. As anticipated,

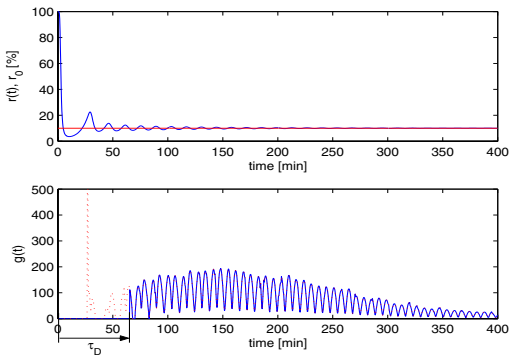

Fig. 4. Plant output (Top) and Falsification signal (bottom) for model (patient) 30 applying controller $\mathcal{C}_1$. Falsification test is activated after τ_D minutes.

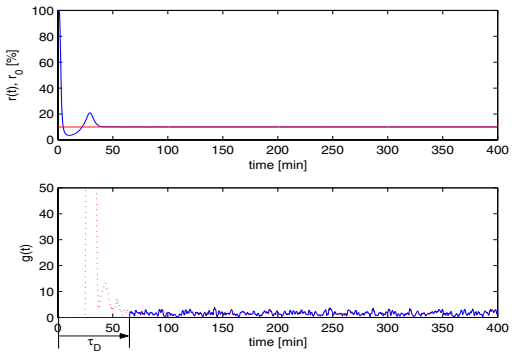

Fig. 5. Plant output (Top) and Falsification signal (bottom) for model (patient) 30 applying controller $\mathcal{C}_4$.

a significant difference in the tracking performance obtained with the two (both stabilizing) controllers is properly revealed by the $g(t)$-index which turns out to violate the stationary threshold fixed at $T_1 = 15$ applying $\mathcal{C}_1$ and is within the threshold ($T_4 = 10$) for $\mathcal{C}_4$.

Notice here that the falsification test is activated only after τ_D (dwell-time $\approx$ 60) min. has elapsed with τ_D satisfying (13). However, by relaxing the assumption in (13) it is possible, on one side to falsify the active controller on the basis of its transient response performance and duration, on the other side to get a falsification response as prompt as possible from the test. This can be obtained by properly designing the two test parameters τ_D and T.

Choice of T: notice that the, analytical or simulative computation of the threshold T prescribed by the theory on controller falsification gives guarantee on the level under which the test variable $g(t)$ will lie once the loop has reached

its stationary state. However, using the $g(t)$-response even during the transient can be useful in order to falsify loops giving unacceptable (too long) transients. In fact, violation of the same "steady state" threshold during transient can be interpreted as a lack of settling to the steady state within a prescribed time (τ_D) and then a too long transient which can be a cause of falsification of the loop.

Choice of τ_D: This indirectly influences the maximum duration admitted for the transient response of the candidate control loop. On the other hand, reduction of τ_D is beneficial for the test's promptness which is crucial in many applications and would allow, in the application under exam to minimize the patient's exposure to drug infusion. As can be seen from Fig. 4 and 5 where the entire evolution of $g(t)$ is reported in dotted line, this can be achieved at the price of fixing a higher threshold T which could correspond to a less strict test. The limit is imposed by the high level of $g(t)$ typically obtained at the early stage of the transient response which could be comparable with the levels obtained for poor steady state performance, thus reducing detection capabilities of the test. A way out is to fix two distinct thresholds for the transient and regime responses.

$$\begin{aligned} g(t) &\lessgtr T' \quad for \;\; t < \tau_D \\ g(t) &\lessgtr T'' \quad for \;\; t \geq \tau_D \end{aligned}$$

The diagrams in Fig. 6 show how the choice of the two parameters τ_D and T influences the test's response. Here controller $\mathcal{C}_1$ is tested in the loop, sequentially connected in feedback with each model in the set. Each model M_j (projected in the controller parameters space) is marked with "$\circ$" or "$+$" if the loop $(M_j/\mathcal{C}_1)$ is respectively falsified or unfalsified over a simulation 10 hours long.
Three different situations are reported. In the first (Fig. 6 top) a dwell time $\tau_D = 60$ min. and threshold $T = 15$ are chosen, *i.e.* the first 60 minutes of test's response are discarded and no decision is taken on the operating loop. Anticipating the test ($\tau_D = 30$ min.), leaving the threshold unchanged (Fig. 6 middle) causes the test to falsify most of the loops as their transient has not yet exhausted even for well performing loops. In order to reestablish a correct partitioning while anticipating the test a higher threshold should be chosen obtaining a partitioning (Fig. 6 bottom) comparable with the first one.
In a similar way, not reported here for space reasons, the models can be tested with the remaining 4 controllers.
Notice that the delay in detection is only partly introduced by the dwell time τ_D. In fact the injection of the initial bolus of anaesthetic, needed for clinical reasons in order to get to the set-point in the shortest time, causes the control input to saturate for an average time of 25 minutes during which the system operates in open loop and hence no question of controller falsification is significant.

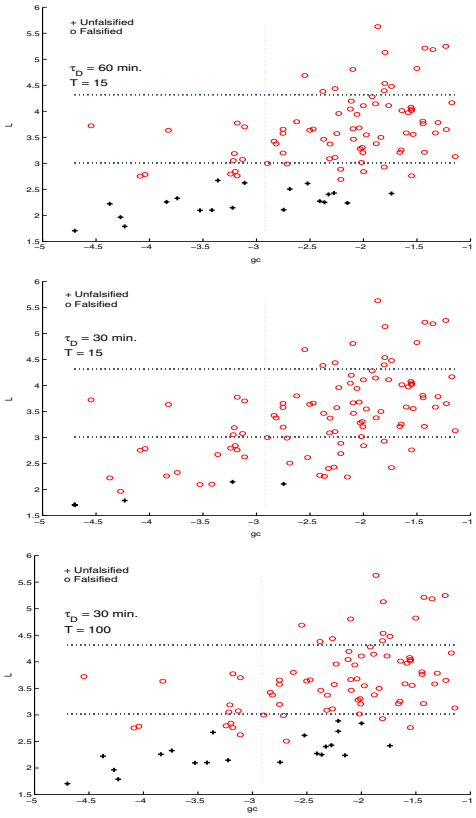

Fig. 6. Influence of the choice of the parameters on the unfalsified ("+")/falsified ("o") loops partitioning: $\tau_D = 60$ min. $T = 15$ (top), $\tau_D = 30$ min. $T = 15$ (middle), $\tau_D = 30$ min. $T = 100$ (bottom).

IV. Two phase test

Simulative experiments show an approximate insensitivity of the falsification test response to the reference level. In fig. 7 a comparison is reported between the partition of unfalsified loops (marked with "$+$") and falsified (marked with "$\circ$") obtained applying respectively a reference $r_0(t) = 10\%$ (left) and $r_0(t) = 95\%$ (right) for controller $\mathcal{C}_1$. As in

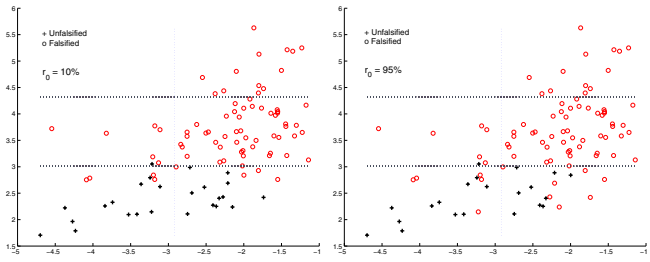

Fig. 7. Comparison between the partition of unfalsified loops (marked with "$+$") and falsified (marked with "$\circ$") for controller $\mathcal{C}_1$ obtained applying respectively a reference $r_0(t) = 10\%$ (left) and $r_0(t) = 95\%$ (right).

the context under exam experiments involve exposition of the plant (patient) to drug infusion which should be obviously minimized, this feature can be exploited in order to design less invasive tests. Consider for example application of Controller Falsification test for controller selection. This would require a sequential application of the different controllers

(5 in the reduced complexity setup) to the patient until one of the controllers is not falsified, *i.e.* data collected from, in the worst case, 5 different candidate controller/patient loops. In this "startup" phase a lower level of muscle relaxation *e.g.* $r_0 = 95\%$ can be chosen as set-point according to the schema in Fig. 8

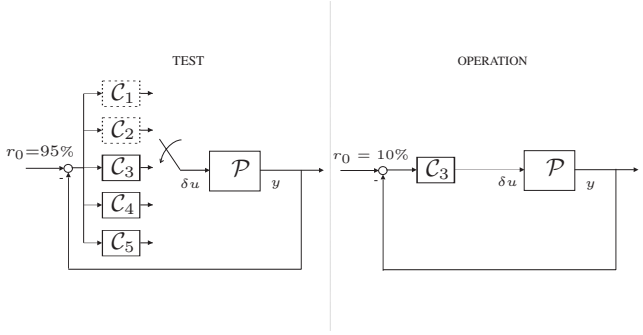

Fig. 8. Two phase test: (left) - noninvasive test ($r_0 = 95\%$) - the controllers are sequentially tested in the loop. The first unfalsified controller ($\mathcal{C}_3$ in figure) is applied with reference $r_0 = 10\%$ (right).

A fundamental feature of this kind of test is that, differently from switching control [3] where a *relative* index is computed in order to choose the best controller *amongst* the available ones, here an *absolute* performance index is provided even telling if one acceptable controller exists at all in the given family for the patient under exam. Due to the potential unpredictability of the whole variability of physiological parameters of the patients and to the criticality of the application, this turns out to be a very positive feature of the test as it safely prevents the application to the patient of a controller without the required performance. Therefore, two possible test's responses are possible:

- one of the controllers is unfalsified for the current patient; this is applied in feedback to the plant with new set-point $r_0 = 10\%$.
- the patient is not in the model family for which controllers are available; a manual drug infusion or a new controller design is needed.

V. Conclusions

A study has been carried out in order to establish whether the falsification test based on the performance index $g(t)$ is applicable in the framework of automatic drug delivery for neuromuscular blockade control. The falsification index has experimentally proven to be a noise insensitive on-line performance measure for which application dependent, noise invariant thresholds are easy to find in order to satisfactorily classify well performing loops from bad ones. Moreover it turns out to be sensitive to poor performance both in the transient and steady state response.

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