IMPROVED ROBUST PERFORMANCE IN A SYSTEM FOR AUTOMATIC ADMINISTRATION OF A VASOACTIVE DRUG

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Abstract: The problem of automatic administration of vasoactive drugs to regulate mean arterial pressure in surgical and postsurgical patients can be considered as a setpoint tracking problem involving a system which is characterised by significant modelling uncertainty in the form of uncertain parameters, unmodelled dynamics and disturbances. Yet, specific levels of performance are required and patient safety must be guaranteed. As part of the development process of a novel Multiple-Model Adaptive Control (MMAC) architecture for this application, we have adopted a mixed-μ synthesis approach to controller design. Simulation results show that the new controllers are capable of improved disturbance rejection and robustness even in the face of large system delays and parametric uncertainty.

1 INTRODUCTION

The cardiovascular system is a critical system of the human body and its operation within a restricted range of operating points is essential to life. Several physiological control pathways naturally exist to respond to external stimuli while ensuring adequate flow rates and pressures in the system (Batzel et al., 2007). Failure to maintain a suitable operating point (cardiovascular decompensation) can lead to severe organ damage or even death. For this very reason, patients at risk of decompensation require continuous monitoring of their condition and possibly administration of suitable drugs to ensure that their cardiovascular system (the plant) does not drift too far from its physiological operating point. In some cases, clinicians may even wish to set and maintain a non-physiological operating point, e.g., a lower blood pressure to facilitate surgery (Furutani et al., 1995).

From an engineering point of view, drug administration to artificially maintain cardiovascular parameters at a desired set point is a closed-loop control problem where the human operator acts as the controller. In current practice, successful stabilisation of a patient relies on the skill and experience of the clinical staff as well as their alertness and ability to identify and respond to early signs of destabilisation. Given the critical nature of this task, the creation of a safe and robust automatic control system capable of maintaining haemodynamic stability in a patient would be of great clinical interest. Such an automatic system could reduce patient risk by removing human error, as well as improve health outcomes and lower healthcare costs through the automation of tasks and the optimisation of drug dosing (Bailey and Haddad, 2005).

The work herein targets the specific issue of regulating mean arterial pressure (MAP) by automatic infusion of a vasodepressor drug, typically sodium nitroprusside (SNP). Administration of vasodepressors is generally required for the treatment of acute hypertension in patients in the intra- and postoperative setting. The idea of applying closed-loop control to automate drug administration in this context has been analysed by several authors over the last two decades (Isaka and Sebald, 1993; Bailey and Haddad, 2005; Bequette, 2007, for a complete review). However, to the authors knowledge, none of the solutions proposed thus far have been commercially successful. We have identified Multiple-Model Adaptive Control (MMAC) as an appropriate framework to tackle this problem. In a MMAC approach, it is assumed that a patient's response can be matched at any time with that of one of several mathematical models included in a model bank. A controller designed for the best matching model is then placed into the feedback loop, where it is expected to yield satisfactory performance.

In recent work (Malagutti et al., 2011), we have

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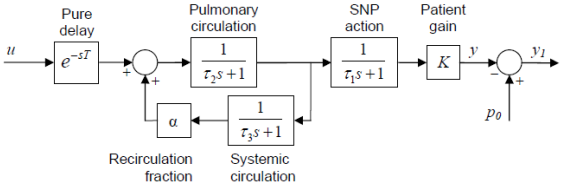

Figure 1: Simplified patient model. T is the pure delay constant; $\tau_1 = 50s$, $\tau_2 = 30s$, $\tau_3 = 10s$ are the time constants of the first-order LTI subsystems; $\alpha = 0.5$ is the recirculation constant; K is the patient gain.

listed a number of issues which could ultimately affect the safety of a MMAC system in the context of MAP control. These can be described either as issues pertaining plant modelling and robust controller design, or intrinsic issues of multiple-model adaptive architectures such as safe controller switching. A framework for the design of Robust MMAC systems has recently been proposed by Fekri et al. (2006) and we aim to evaluate its applicability to this biomedical problem.

This paper presents our initial results in addressing plant modelling and robust controller design issues. More specifically, we question the range of uncertainty which should be included in the plant model and utilise a μ synthesis controller design technique to achieve robust performance in the face of a large parametric uncertainty set and system delays.

In Section 2, we review the first MMAC architecture presented for this application (Martin et al., 1987) and present some of its potential shortcomings. Section 3 introduces a new system structure and describes the controller design process. Section 4 presents the results of a numerical simulation which highlights the results of our design. Finally, Section 5 discusses the results and presents open questions and issues.

2 PROBLEM DESCRIPTION

2.1 The Simplified Patient Model

The model describing the patient response to SNP infusion used in Martin et al. (1987) is a modified version of the linear model with delay of Slate (Slate et al., 1979) and is shown in Figure 1. The transfer function of this system is given by

$$\frac{Y(s)}{U(s)} = e^{-sT} \frac{K(\tau_3 s+1)}{((\tau_3 s+1)(\tau_2 s+1)-\alpha)(\tau_1 s+1)} \quad (1)$$

$$Y_1(s) = p_0 - Y(s), \quad (2)$$

where $U(s)$ is the rate of administration of the drug, $Y(s)$ is the drop in pressure caused by the drug, the output $P(s)$ of the patient model is MAP, and p_0 is the patient's "natural" blood pressure, i.e., the value of MAP which the patient would display in the absence of pharmacological intervention. All model parameters are deemed constant with the exception of the gain parameter K, which can range between 0.25 and 9.5mmHg/(ml/hr) and the delay constant T which can take any value up to 50s.

Table 1: Model bank gain values and range of true plant gains covered. SNP concentration 200 $\mu g/ml$.

Model no. i	Model Gain K_i (mmHg/(ml/h))	To suit Plant Gain K (mmHg/(ml/h))
1	0.33	0.25 – 0.47
2	0.62	0.47 – 0.89
3	1.15	0.89 – 1.65
4	2.10	1.65 – 2.96
5	3.69	2.96 – 5.02
6	6.06	5.02 – 7.82
7	9.03	7.82 – 10.86

2.2 Closed-loop MMAC

The MMAC architecture of Martin et al. (1987) is shown in Figure 2. In the closed-loop system, the pressure output y_1 of the plant (patient) is compared with that of a bank of 7 models designed using the system in (1). See Table 1 for a list of gain values used. On the basis of the difference (residuals) between the patient output and the model bank outputs, an iterative computation of weights is carried out. Weights are assigned to the controllers in the controller bank so that the controller corresponding to the model which is most representative of the plant receives the largest weight. The control signal u is given by the weighted average of the controller bank outputs. The effect of delay is compensated by utilising a bank of 7 Smith's predictors (one per each model in the bank) having the following transfer function:

$$\frac{Y^*(s)}{U(s)} = \frac{K_i(s+0.033)}{500(s+0.1194)(s+0.02)(s+0.014)}(1-e^{-sT^*}) \quad (3)$$

$$Y_{1i}^*(s) = p_0 - \frac{Y^*(s)}{U(s)}, \quad (4)$$

where K_i is the value of K for the ith model in the model bank as in (1) and T^* is the best available estimate of the plant delay. The closed loop also includes three nonlinear control signal limiters which will not be discussed here due to space limitations and we refer the reader to other works (Martin et al., 1987; Malagutti et al., 2011).

The control performance requirements for the closed-loop system are a maximum rise time of 10 minutes in the presence of a step setpoint change, a

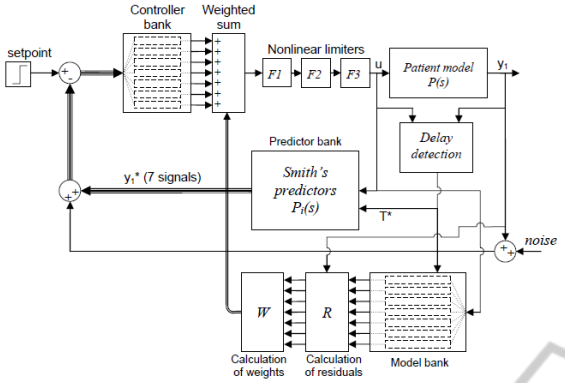

Figure 2: The MMAC architecture of (Martin et al., 1987). The setpoint is expressed as the required MAP. Thicker arrows and lines indicate vector signals.

maximum overshoot of 10 mmHg and a limit on drug infusion rate of 600μg/(kg·h).

2.3 Modelling and Robustness Issues

In Malagutti et al. (2011), the closed-loop system of Figure 2 was simulated under challenging operating conditions and instances of undesirable behaviour were generated. A number of these were caused by the erroneous identification of the plant, which led to the insertion of an inadequate controller in the loop. In this paper, we neglect issues associated with plant-model matching and assume that the correct plant model is identified, that is, the controller associated with the appropriate gain range (Table 1) is placed in the feedback loop at all times. We focus on issues of plant and uncertainty modelling, which, in our opinion, were oversimplified in earlier approaches (Martin et al., 1987) leading to the design of controllers which are not sufficiently robust. We have identified three key aspects:

- the use of a Smith's Predictor architecture causes stability and performance to depend on an accurate estimate of the plant delay, which may not be guaranteed;
- the assumption that all parameters except gain K are deemed constant may be too coarse;
- the assumption that parameter p_0 in equation (2) is deemed constant may be unsuitable.

In Martin et al. (1987), it is asserted that delay can be estimated, and that this estimation can take place at each setpoint change of 20 mmHg or more. We note that this poses a problem as the objective of the control system is to maintain blood pressure stable and therefore multiple setpoint changes of considerable amplitude (20 mmHg is a very significant change in MAP) would be undesirable. Also, there is no protection against a possible change in the delay constant between setpoint changes. Here, we design controllers which ensure robust performance over the whole range of possible time delays.

It is difficult to critically evaluate whether the assumption of considering constant plant parameters with the exception of K is a reasonable one, as the three time constants condense the behaviour of several physiological systems. The parameter α, however, has a clear pharmacodynamic significance and represents the extent to which the drug is removed from the bloodstream. With the aim of achieving the safest possible design, we deem it entirely plausible that this value may undergo some changes during the course of a procedure. Indeed, a different value ($\alpha = 0.4$) has been used elsewhere (Slate et al., 1979). In Martin et al. (1987), the choice of considering K as the only uncertain model parameters was justified by stating that all changes to other parameters may be assimilated as changes in K. We disagree with this as α does affect the position of the system poles in (1) and therefore may impact on closed-loop stability and performance. Figure 3*(a)* shows that, using the control architecture of Martin et al. (1987), undesirable oscillations may occur in a system where the time constant has not been identified properly and the recirculation constant has changed, even when one assumes that the correct controller is placed in the loop.

Finally, the architecture of Martin et al. (1987) assumes that a "natural" value of MAP (p_0) can be determined for each patient. While this might be

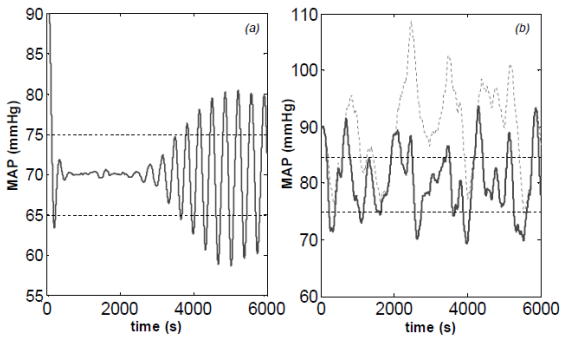

Figure 3: Instances of undesirable behaviour from the system of Martin et al. (1987) (horizontal dashed lines indicate $\pm$5mmHg steady state error). *(a)*: oscillations caused by mismatch between the true plant and the model used in the Smith's predictor (T^* =10s vs T increasing linearly from 10 s to 50 s between t=1000 s and t=2600 s; true α of 0.6 instead of 0.5; $K = 0.47$ vs $K^* = 0.33$). *(b)*: inability to track the desired MAP in the presence of changes in p_0 (exact match between true plant and Smith's predictor model; fine dashed curve represents p_0 with added low-frequency SPD within the range $\pm$20 mmHg).

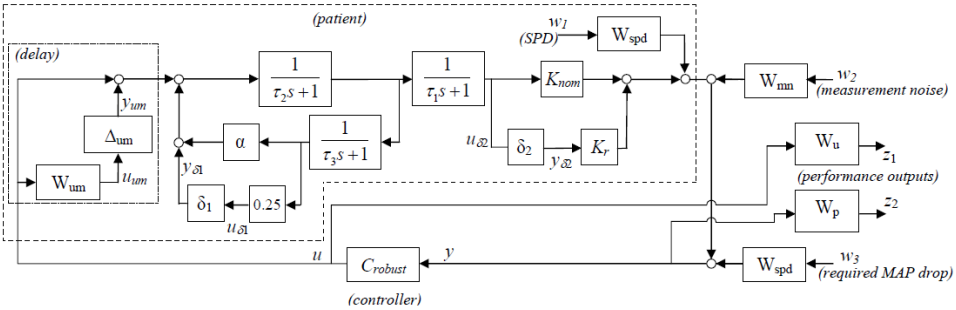

Figure 4: The system model used for robust controller design.

true in baseline conditions, events including renin-angiotensin activation, breathing, trauma-induced vasoconstriction and loss of blood volume through bleeding (Batzel et al., 2007) can shift the natural operating point of the cardiovascular system thereby affecting p_0. Furthermore, this change cannot be detected through the sensor measurements, which means that over time differences may arise between the values of p_0 of equations (2) and (4), affecting the error signal which is fed to the controller and thereby degrading the control action. We note that a clinically safe system should be able to contain these dynamics and we refer the reader to Figure 3*(b)*, which shows the results of a simulation in which we added a so called set-point disturbance (SPD) signal (generated as filtered gaussian noise) to p_0. The system set-up of Martin et al. (1987) clearly fails to stabilise the patient in these conditions, even when all other plant parameters (α, K and T) are exactly matched in the Smith's predictor.

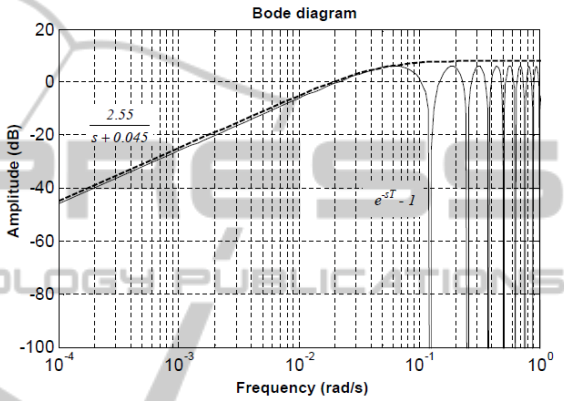

Figure 5: Upper bound (dashed) for the multiplicative modelling error (solid) introduced by treating the patient delay as an unmodelled dynamic.

3 DESIGNING FOR ROBUST PERFORMANCE

3.1 Uncertainty Model and Performance Requirements

The block diagram shown in Figure 4 includes the patient model of Figure 1 and introduces a description of parametric uncertainty for the gain and recirculation parameters:

$$\alpha = 0.5 + 0.25\delta_1,\ K = K_{nom} + K_r\delta_2,$$
$$\delta_1, \delta_2 \in \mathbb{R}, |\delta_1| \leq 1, |\delta_2| \leq 1,$$

which is equivalent to assuming that $\alpha = (0.5 \pm 0.25)$ and $K = (K_{nom} \pm K_r)$ where K_{nom} represents the nominal value of the gain parameter and K_r is half the width of the uncertainty range.

Delay is taken into account as an unmodelled dynamic of the system. As the maximum expected value of the delay is $T = 50$s, neglecting it would introduce a multiplicative modelling error of $e^{-sT} - 1$. This error can be bounded by the high-pass transfer function W_{um} as shown in Figure 5. In Figure 4, the unmodelled dynamic is represented by the blocks surrounded by the dotted box. Its transfer function is

$$1 + \Delta_{um} \cdot W_{um},\ \Delta_{um} \in \mathcal{H}_\infty,\ \|\Delta_{um}\|_\infty \leq 1,$$

which is a conservative representation of all possible patient delay dynamics for $T \leq 50$ s.

In Figure 4, the control problem is redefined so that controller design via μ synthesis can be performed. In the new definition, we identify a signal called set-point disturbance, which is added to the output of the plant and represents the possible changes in the value of p_0 as discussed in Section 2. These are assumed to be in the form a low-frequency signal and are generated using white noise ($w_1 : \|w_1(j\omega)\|_\infty \leq 1$) filtered by the LTI system W_{spd} (Table 2). The same filter is also used as a command prefilter for the reference signal ($w_3 : \|w_3(j\omega)\|_\infty \leq 1$) set by the clinician (we deem it reasonable to assume the reference as slowly varying), which indicates the required drop from the patient's baseline MAP, as measured at the beginning of the procedure.

The transfer function W_{spd} is a low-pass transfer function with a steady-state gain of 32dB as a range of ±40mmHg from baseline was deemed sufficient to cover all possible setpoint requirements. The pole location is such that the filter step response has a settling time of less then 10 min, in order to comply with the command following requirements of Section 2.2. There is no specific reason other than computational convenience behind our decision to use W_{spd} as both a disturbance colouring filter and a command prefilter.

Measurement noise is modelled as a random gaussian signal (w_2) filtered by high-pass filter W_{mn} (Table 2). This generates a random, high-frequency noise signal of magnitude ≤12 dB (±4 mmHg).

The reformulation of Figure 4 also includes two weighting transfer functions which reflect the performance requirements. The weighting function W_p is the performance weight placed on the error signal ($W_p : \|W_p(j\omega)Y(j\omega)\|_\infty \leq 1$); it imposes a maximum error of 6 dB (±2 mmHg) at steady state and 22 dB (±12.5 mmHg) at higher frequencies. The weighting function W_u places constrains the control signal ($W_u : \|W_u(j\omega)U(j\omega)\|_\infty \leq 1$) in terms of maximum amplitude at low frequency (200 ml/hr, roughly equivalent to the toxicity threshold for a 65 kg patient) and penalises high-frequency control dynamics. This requirement arises from the consideration that administration would be provided through a motorised infusion pump, which is likely to be unable to respond to fast changes in infusion rate demands.

3.2 Controller Design via μ Synthesis

The new controllers were designed using the technique of mixed-μ synthesis. Due to the involved nature of the μ synthesis approach, a detailed description will not be provided here and interested readers may consult specialised texts (Zhou et al., 1995). For the scope of this paper it will be sufficient to explain that the *structured singular value* μ—a commonly used tool in $\mathcal{H}_\infty$ optimal control—is defined as

$$sup_{\omega\in\mathbb{R}^+}\mu(\mathcal{M}(j\omega)) = \frac{1}{sup_{\omega\in\mathbb{R}^+}\inf_{\Delta(j\omega)}\{\overline{\sigma}(\Delta) : \det(I-\mathcal{M}\Delta)=0\}} \quad (5)$$

Table 2: Transfer function (TF) reference table.

Block name	TF	Purpose
W_{spd}	$\frac{40}{(125s+1)^2}$	SPD and reference filtering
W_{mn}	$\frac{s}{0.25s+0.075}$	Measurement noise filter
W_p	$\frac{(700s+1)^2}{(2500s+1.4)^2}$	Weighting TF (output signal)
W_u	$\frac{20s+200}{80s+1}$	Weighting TF (control signal)

where $\overline{\sigma}$ indicates the maximum singular value and the $\mathcal{M}$–Δ structure is a particular form of the interconnected system as shown in Figure 6, and in our particular problem

$$\Delta = \begin{pmatrix} \delta_1 & 0 & 0 & 0 \\ 0 & \delta_2 & 0 & 0 \\ 0 & 0 & \Delta_{um} & 0 \\ 0 & 0 & 0 & \Delta_p \end{pmatrix}, \text{ where } \begin{cases} \Delta_p \in \mathbb{C}^{3\times 2} \\ ||\Delta_p||_\infty \leq 1 \end{cases}.$$

In general terms, μ represents the inverse of the minimum increase in plant uncertainty which would result in the system being unable to meet the required specifications with a particular controller C inserted in the loop. A result derived from the small gain theorem states that the closed-loop system is capable of robust performance if $\mu \leq 1$ (Gu et al., 2005).

The μ synthesis approach involves an iterative search, among the set of stabilising controllers C_s, to identify the controller which achieves the largest robustness margin, i.e., the smallest value of μ.

$$\inf_{C\in C_s} sup_{\omega\in\mathbb{R}^+}\mu(\mathcal{M}(j\omega)) \quad (6)$$

Software tools to conduct μ synthesis are available as part of the Matlab Robust Control Toolbox. Specifically, we use the *mixed-*μ synthesis algorithm, which can take advantage of the fact that the uncertainty space of some of the model parameters is real and not complex. This reduces, to some extent, the conservativeness of the resulting controller design.

3.3 Controller Design Results

As the technique of μ synthesis assists in the design of controllers capable of yielding robust performance, a key question is whether multiple controllers are actually required in order to meet the requirements of this control problem. To address this, we used an approach similar to the design of the controller bank in the Robust MMAC architecture (Feakri et al., 2006). We programmed an iterative Matlab algorithm to determine the maximum achievable performance of the system as a function of the range of plant uncertainty

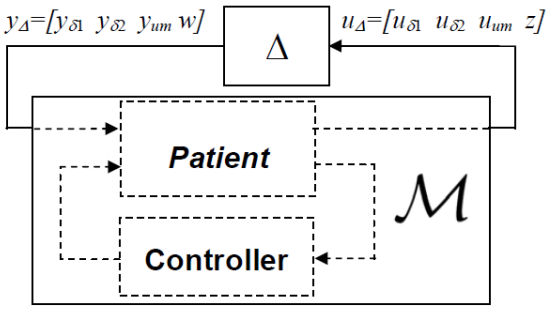

Figure 6: $\mathcal{M}$–Δ interconnected structure for μ synthesis. Note $w = [w_1\ w_2\ w_3]$, $z = [z_1\ z_2]$.

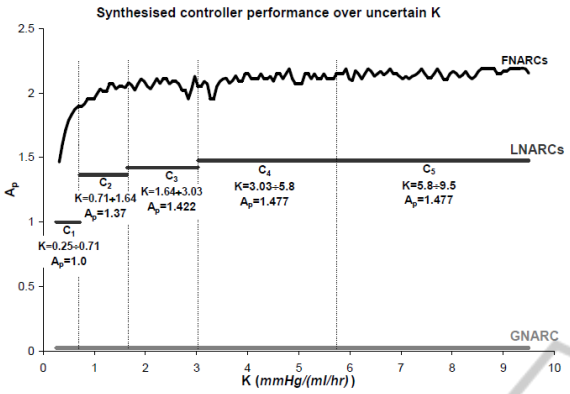

Figure 7: Results of GNARC, FNARC and LNARC controller design instances. The graph shows the maximum achievable performance A_p as a function of the uncertainty range of K considered.

considered. Achievable performance is rated according to a scalar parameter A_p which multiplies the performance weight, i.e., $W_p^* = A_p \cdot W_p$. The algorithm operates as follows:

1. set A_p=1;
2. set up the interconnected system of Figure 4, include the required amount of uncertainty and use W_p^* as the performance weight on the error signal;
3. run the mixed-μ synthesis tool on the system generated at step 2;
4. if the value of μ is jut below unity ($0.985 \leq \mu \leq 1$), A_p is deemed to represent the maximum achievable performance and the controller synthesised at step 3 can ensure that performance level is met, otherwise, A_p is increased (for $\mu \leq 0.985$) or decreased (for $\mu \geq 1$) as required and another iteration (starting at step 2) takes place.

Since the performance weights W_p and W_u represent the required minimum performance for the system, a final value of $A_p \geq 1$ means that a controller exists such that the system can exceed the requirements, while $A_p < 1$ indicates that μ synthesis cannot produce a suitable controller to meet the required performance over the considered uncertainty set.

All runs of our algorithm included the full complex uncertainty associated with the delay (Section 3.1) and the full range of real parametric uncertainty for α, while different subsets of the uncertainty set of K were considered as described below. This was done to obtain comparable results with Martin et al. (1987), where gain is the only varying parameter.

Figure 7 shows the three fundamental design cases which we used to evaluate a trade-off between the number of controllers and the maximum achievable A_p as a function of the breadth of the uncertainty subset of K considered:

- a global non-adaptive robust controller (GNARC), i.e., a controller able to provide robust performance over the full uncertainty range of K. The maximum A_p achieved was 0.026, indicating that a single-controller architecture would not meet the requirements of this problem;
- fixed non-adaptive robust controllers (FNARCs), i.e., multiple controllers (ideally, infinitely many), each designed to maximise performance for a point value of K (no uncertainty on K). The results of this design case are representative of the maximum achievable performance with a multiple-controller system. It is clear from Figure 7 that the such an ideal system would be able to meet and even exceed the required level of performance, more notably so in the high-K region of the uncertainty space;
- local non-adaptive robust controllers (LNARCs), i.e, controllers capable of providing satisfactory performance over non-infinitesimal subsets of the uncertainty space of K. This design case is a "middle ground" between the GNARC and the FNARCs. A controller design covering a larger uncertainty subset will result in a system with inferior performance. It is up to the designer, therefore, to strike a suitable compromise between controller bank complexity (number of controllers) and system performance (maximum A_p). In the results shown, we defined suitable performance as either A_p=1 (the minimum required) or 60% of the minimum FNARC over the corresponding uncertainty subset, whichever the greatest. Five controllers were required to cover the whole uncertainty space of K. The reader may wish to compare the controller design results of Figure 7 with those of Martin et al. (1987) listed in Table 1.

4 NUMERICAL SIMULATION

A number of numerical simulations were performed using Simulink in order to evaluate the performance of the newly synthesised controllers. Here we describe a "stress test", which includes and combines the situations which were shown in Section 2 to determine unsuitable system behaviour, in order to compare the performance of traditional PI controllers (Martin et al., 1987) with that of the new controllers.

We designed a sample case of a patient undergoing a lengthy operation of several hours (330min). Since the model identification and controller assignment as-

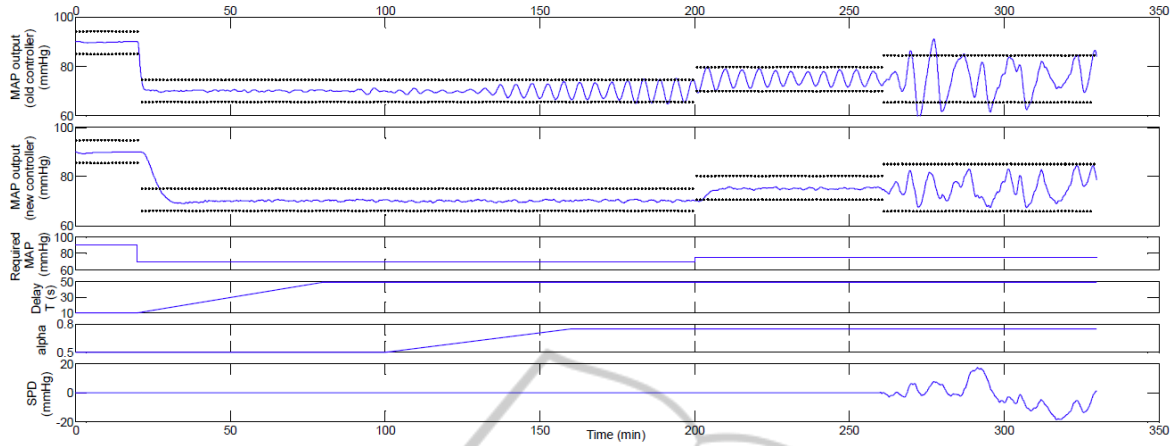

Figure 8: Results of the numerical simulation. The dotted lines indicate the acceptable MAP error interval of ±5 mmHg in the absence of set point disturbances and ±10mmHg otherwise.

pects of MMAC were not the focus of this work, the gain parameter $K = 7.7$ was assumed fixed throughout the operation so that the correct controller could be determined *a priori* (C_6 in Table 1, C_5 in Figure 7). At t=0, the patient's MAP was 90mmHg and the delay constant was correctly estimated at T=T^*=10s. After 20min, a step pressure drop (-20mmHg) was required by the clinician. Over the following 60min, a slow linear drift in patient delay was introduced, increasing to $T = 50$s while the T^* parameter of the Smith's predictor was not changed. After 20min of steady operation, a slow change in α was introduced, increasing the parameter from 0.5 to 0.75 over 60 minutes. A step reference change (+5mmHg) was introduced at 200 minutes. Finally, during the last 70 minutes of the procedure, a random low-frequency SPD signal in the range ±20mmHg was applied. Sensor noise was present throughout and modelled as gaussian white noise (mean 0mmHg, variance 4mmHg).

The simulation is summarised in Figure 8, where we also show a comparison of the results of the system with the two different types of controllers. Since the simulation includes a significant amount of disturbance, the steady state error bound of ±5mmHg cannot apply. Disturbance rejection was deemed satisfactory if fluctuations in the measured MAP are contained within ±10mmHg, which is the prescribed limit in overshoot introduced in Section 2.1. The results show that in cases where the mismatch between the true plant and the nominal model used in the controller design becomes significant, the system of Martin et al. (1987) may display oscillations, as also shown in Figure 3. No significant oscillations occurred with the new controllers independently of changes in the delay constant T and the recirculation parameter α or the requirement for small setpoint changes. In the presence of fluctuations in the patient's baseline MAP, the new controllers are more effective in containing the fluctuations within a reasonable ±10mmHg, while the old system may reach undesirably low values in certain circumstances.

5 DISCUSSIONS AND FUTURE WORK

In control applications such as this one, where considerable variability may exist among subjects and even within one subject over time, in the presence of disturbances which may render off-line system identification unfeasible and on-line identification unreliable, a multiple-model adaptive control architecture is advantageous. It offers the possibility of describing a time-varying system as the interpolation of locally valid linear models, thus allowing the control designer to exploit advanced controller design techniques for linear systems without sacrificing generality in the description of the underlying process. Key issues in MMAC are the definition of the breadth of uncertainty to be included in the bank of models, and the number of models and controllers required to deliver the desired performance for all possible combinations of the uncertain parameters.

The approach adopted herein has allowed us to methodically address whether the degree of uncertainty involved in the problem of automatic administration of SNP would benefit from a multiple controller architecture. The answer to that question is clearly affirmative. Not only have we clarified that robust performance cannot be achieved with a GNARC, but we also formalised that a potential performance increase of up to 100 fold (cf. values of A_p=0.02 for

GNARC and A_p=2.0 for FNARCs) can be achieved over certain subsets of the uncertainty range of K using adaptive control. A trade-off is clearly observable between the number of controllers and the maximum achievable value of the performance index A_p. We were able to meet or exceed the robust performance specifications and cover an even larger uncertainty space than that of Martin et al. (1987) with a smaller number of controllers (5 vs 7).

We have argued that overly simplified physiological assumptions may lead to models which fail to describe the real plant with sufficient accuracy, increasing the risk of degraded performance or even instability. In this paper, we have reiterated a few examples of this and we have reasoned, on the basis of simple physiological knowledge, that additional uncertainty in the parameters α and T should be accounted for. As risk minimisation is a paramount aspect of medical technology (Malagutti et al., 2011), and perhaps one of the key reasons behind the lack of success of the one and only ever commercialised device for this application, the IVAC Titrator (IVAC Corporation, San Diego, CA, USA) (Bequette, 2007), we believe that improved robustness has an important role to play in making automatic drug administration systems safer and more widely acceptable in critical clinical settings. In this context, the use of μ synthesis as a controller design technique represents an improvement over previous approaches as it offers a mathematical guarantee of robust closed-loop stability and performance over the expected range of uncertainty.

Despite the promising results, the proposed adaptation of a robust MMAC architecture to this drug delivery problem will require further work before it can be proposed to a clinical audience. Effective stabilisation of a patient using the safe controller designs presented herein relies on the assumption that the correct patient gain K can be identified and the corresponding controller placed in the loop at all times. This is a critical assumption which has not been analysed in detail here. Indeed, Malagutti et al. (2011) have advocated caution against scenarios of instability or poor performance caused by the insertion of the wrong controller in the loop as a result of incorrect model identification. The issues of reliably matching the plant with a candidate model and safely placing a suitable controller in the loop (avoiding the insertion of inappropriate controllers or placing a safe upper bound on the time they can remain in the loop for) are critical in MMAC systems and will be investigated as the next steps in our research towards a complete and safe control architecture for this medical application.

A final remark concerns the focus of the control task on blood pressure, which is only one of a number of parameters which characterise the state of the cardiovascular system. In this context, stabilisation of MAP alone may constitute an insufficient clinical outcome. Following further consultation with clinical professionals, future work may need to consider multivariable models which include other key cardiovascular variables (cardiac output, vascular resistance, atrial pressures, etc.) and other administrable drugs. Some experimental work exists in the literature addressing simultaneous control of MAP and cardiac output (Yu et al., 1992; Rao et al., 2001), however, to the authors' knowledge, MMAC architectures have not yet been utilised for this purpose. The same approach presented here has the potential to be extended, with minor variations, to handle a multivariable case.

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